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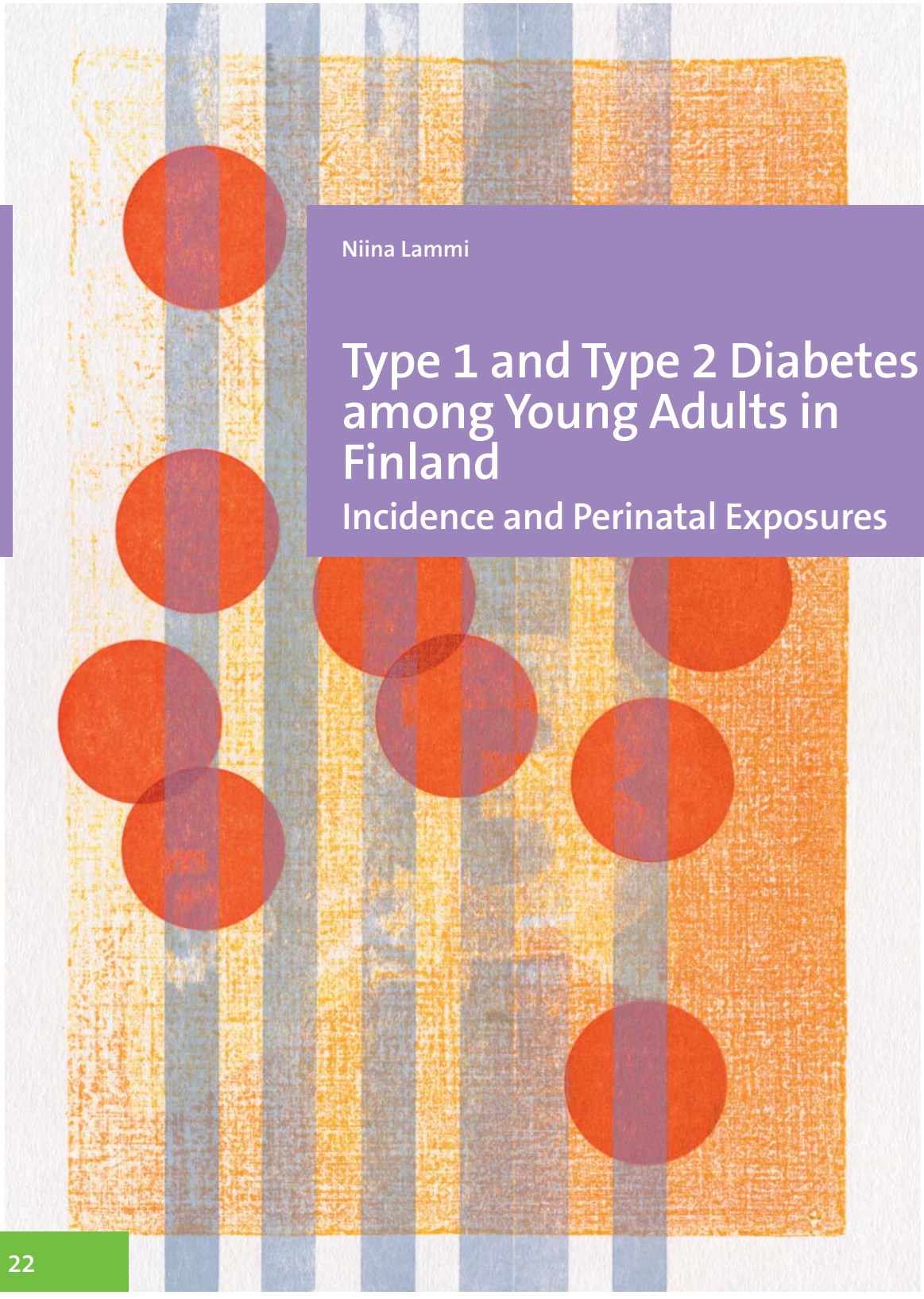

RESEARCH

Niina Lammi

Type 1 and Type 2 Diabetes among Young Adults in Finland

Incidence and Perinatal Exposures

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Incidence and Perinatal Exposures

ACADEMIC DISSERTATION

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Supervised by

Professor Johan Eriksson, MD, Ph.D.
Department of General Practice and Primary Health Care
University of Helsinki
Helsinki, Finland and
Department of Chronic Disease Prevention
National Institute for Health and Welfare
Helsinki, Finland

and

Docent Marjatta Karvonen, MSc, Ph.D.
Department of Chronic Disease Prevention
National Institute for Health and Welfare
Helsinki, Finland

Reviewed by

Docent Elina Hyppönen, MSc, MPH, Ph.D.
Tampere School of Public Health
University of Tampere
Tampere, Finland and
Centre for Paediatric Epidemiology and Biostatistics
UCL Institute of Child Health
London, UK

and

Docent David Laaksonen, MD, MPH, Ph.D.
Department of Medicine
University of Kuopio
Kuopio, Finland

Opponent

Professor Leo Niskanen, MD, Ph.D.
Department of Medicine
University of Kuopio
Kuopio, Finland

To Lauri and Eino

Abstract

Niina Lammi. Type 1 and Type 2 Diabetes among Young Adults in Finland.
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Diabetes mellitus is one of the major public health problems worldwide. Unlike the old terms juvenile-onset and adult-onset diabetes suggest, both type 1 diabetes (T1DM) and type 2 diabetes (T2DM) can be diagnosed at any age. However, the epidemiology of young adult-onset T1DM and T2DM among Finns is unknown. In addition, the recently implicated risk factors for T1DM and T2DM related to body size at birth and childhood growth need to be studied among young adults. This study aimed to examine the incidence of young adult-onset T1DM and T2DM among Finns, and to explore the possible risk factors for young adult-onset T1DM and T2DM that occur during the perinatal period and childhood.

In the first two studies (I-II), the incidence of young adult-onset diabetes was examined among 15-39-year-old Finns during the years 1992-2001. Information on the new diagnoses of diabetes was collected from four sources: standardized national reports filled in by diabetes nurses, the Hospital Discharge Register (National Development Centre for Welfare and Health), the Drug Reimbursement Register, and the Drug Prescription Register (Social Insurance Institute). The type of diabetes was assigned using information obtained from these four data sources, and when necessary, medical statements were reviewed in order to confirm the diagnosis. The results showed that the incidence of T1DM among 15-39-year-old Finns was 18 per 100,000/year, and there was a clear male predominance in the incidence of T1DM. The incidence of T1DM increased on average 3.9% per year during 1992-2001. The incidence of T2DM among young Finnish adults was 13 per 100,000/year, and it displayed an increase of as much as 4.3% per year during the study period.

In the studies III-V, the effects of perinatal exposures and childhood growth on the risk for young adult-onset T1DM and T2DM were explored in a case-control setting. Individuals diagnosed with T1DM (n=1,388) and T2DM (n=1,121) during the period 1992-1996 were chosen as the diabetes cases for the study, and two controls matched by age, place of birth, and sex were chosen for each case from the National Population Register. Data on the study subjects' parents and siblings (including date of birth) was obtained from the National Population Register. The study subjects' original birth records and child welfare clinic records were traced nationwide. The results of the case-control study showed that the risk for young

adult-onset T2DM was the lowest among the offspring of mothers aged about 30 years, whereas the risk for T2DM increased towards younger and older maternal ages. Birth orders second to fourth were found protective of T2DM. In addition, the risk for T2DM was observed to decrease with increasing birth weight until 4.2 kg, after which the risk began to increase. In examining growth rate after birth, it was observed that a high body mass index (BMI) at the BMI rebound between ages 3-11 years substantially increased the risk for T2DM, and the excess weight gain in individuals diagnosed with T2DM began in early childhood. Unlike in T2DM, maternal age, birth order, or body size at birth had no effect on the risk for young adult-onset T1DM. Instead, individuals with T1DM were observed to have a higher maximum BMI before the age of 3 than their control subjects.

In conclusion, the increasing trend in the development of both T1DM and T2DM among young Finnish adults is alarming. The high risk for T1DM among the Finnish population extends to at least 40 years of age, and at least 200-300 young Finnish adults are diagnosed with T2DM every year. Growth during the fetal period and childhood notably affects the risk for T2DM. T2DM prevention should also target childhood obesity. Rapid growth during the first years of life may be a risk factor for late-onset T1DM.

Information on the incidence of diabetes among young adults establishes a basis for future epidemiological research. A more profound understanding of the risk factors concerning T1DM and T2DM will aid more precise risk profiling and may lead to a better understanding of the pathogenesis.

Keywords: birth order, birth weight, growth, incidence, maternal age, type 1 diabetes, type 2 diabetes, young adults

Tiivistelmä

Niina Lammi. Type 1 and Type 2 Diabetes among Young Adults in Finland. Incedence and Perinatal Exposures. [Tyypin 1 ja tyypin 2 diabetes suomalaisilla nuorilla aikuisilla. Ilmaantuvuus ja perinataaliset altisteet]. National Institute for Health and Welfare (THL), Tutkimus 22. 144 sivua. Helsinki 2009.
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Sokeritauti (diabetes mellitus) on yksi maailman vakavimmista kansanterveysongelmista. Toisin kuin entisistä termeistä nuoruusiän ja aikuisiän diabetes voisi päätellä, tyypin 1 diabetes ja tyypin 2 diabetes voivat puhjeta missä iässä tahansa. Sekä tyypin 1 diabeteksen että tyypin 2 diabeteksen epidemiologia suomalaisilla nuorilla aikuisilla on kuitenkin selvittämättä. Lisäksi viime aikoina esitettyjä syntymäkokoon ja lapsuuden kasvuun liittyviä riskitekijöitä tulisi tutkia myös nuorten aikuisten ikäryhmässä. Tämän tutkimuksen tavoitteena oli selvittää tyypin 1 ja tyypin 2 diabeteksen ilmaantuvuutta suomalaisilla nuorilla aikuisilla ja arvioida mahdollisia perinataalikaudella ja lapsuudessa esiintyviä nuorten aikuisten diabeteksen riskitekijöitä.

Kahdessa ensimmäisessä osatyössä (I-II) tutkittiin tyypin 1 ja tyypin 2 diabeteksen esiintyvyyttä 15-39-vuotiailla suomalaisilla vuosina 1992-2001. Tiedot uusista diabetestapauksista kerättiin diabeteshoitajien täyttämillä vakioiduilla lomakkeilla, sairaalapoistorekisteristä (STAKES), lääkekorvausrekisteristä (Kansaneläkelaitos) ja erityiskorvausoikeusrekisteristä (Kansaneläkelaitos). Diabeteksen tyyppi määritettiin käyttämällä diagnoosi- ja lääkitystietoja, ja tämän lisäksi tyyppi varmistettiin tarvittaessa lääkärinlausunnoista. Tulokset osoittivat, että tyypin 1 diabeteksen ilmaantuvuus suomalaisilla nuorilla aikuisilla oli 18 per 100 000/vuosi, ja että tyypin 1 diabeteksen sairastuneissa oli selkeä miesenemmistö. Tyypin 1 diabeteksen ilmaantuvuus lisääntyi keskimäärin 3,9% vuodessa vuosina 1992-2001. Tyypin 2 diabeteksen ilmaantuvuus suomalaisilla nuorilla aikuisilla oli 13 per 100 000/vuosi ja tyypin 2 diabetes lisääntyi jopa 4,3% vuosittain tutkitulla ajanjaksolla.

Osatöissä III-V selvitettiin perinataalisten tekijöiden ja lapsuuden kasvun vaikutuksia nuorten aikuisten tyypin 1 ja tyypin 2 diabeteksen ilmaantuvuuteen käyttäen tapaus-verrokki asetelmaa. Ajanjaksolla 1992-1996 diagnosoidut 1388 tyypin 1 diabeetikkoa ja 1121 tyypin 2 diabeetikkoa valittiin diabetestapauksiksi, ja jokaiselle tapaukselle valittiin kaksi syntymäpäivän, sukupuolen ja syntymäpaikan suhteen kaltaistettua kontrollihenkilöä väestörekisteristä. Tiedot (sisältäen syntymäpäivät) tutkimushenkilöiden vanhemmista ja sisaruksista saatiin väestörekisteristä. Tutkimushenkilöiden alkuperäiset synnytyskertomukset ja

lastenneuvolakortit etsittiin arkistoista maanlaajuisesti. Tapaus-verrokkitutkimuksen tulokset osoittivat, että riski sairastua nuorena aikuisena tyypin 2 diabetekseen oli matalin noin 30-vuotiaiden äitien lapsilla ja taudin riski kasvoi äidin iän nuorentuessa tai vanhentuessa. Lisäksi perheen toisena, kolmantena tai neljäntenä syntyneillä lapsilla todettiin olevan pienempi riski sairastua tyypin 2 diabetekseen kuin esikoisella. Nuorten aikuisten tyypin 2 diabeteksen riski väheni syntymäpainon suurentuessa 4,2 kg asti, minkä jälkeen riski alkoi jälleen lisääntyä. Tutkimalla syntymänjälkeistä kasvua havaittiin, että korkea painoindeksi 3-11 vuoden iässä, hetkellä jolloin lapsen painoindeksi taittuu nousuun, lisäsi huomattavasti riskiä sairastua tyypin 2 diabetekseen nuorella aikuisiällä. Liiallinen painonnousu henkilöillä, jotka sairastuvat tyypin 2 diabetekseen, alkoi jo varhain lapsuusiässä. Toisin kuin tyypin 2 diabeteksessa äidin ikä, syntymäjärjestys tai syntymäkoko eivät vaikuttaneet riskiin sairastua tyypin 1 diabetekseen nuorella aikuisiällä. Sen sijaan henkilöillä, jotka sairastuivat tyypin 1 diabetekseen, painoindeksin huippu oli korkeampi alle 3-vuotiaana kuin heidän verrokeillaan.

Yhteenvetona voidaan todeta, että sekä tyypin 1 että tyypin 2 diabeteksen ilmaantuvuuden nousu suomalaisilla nuorilla aikuisilla on hälyttävää. Suomalaisessa väestössä korkea riski sairastua tyypin 1 diabetekseen jatkuu ainakin 40 vuoden ikään, ja vähintään 200-300 suomalaista nuorta aikuista sairastuu tyypin 2 diabetekseen vuosittain. Sekä sikiöaikainen että lapsuusiän kasvu vaikuttavat huomattavasti tyypin 2 diabeteksen riskiin. Tyypin 2 diabeteksen ehkäisemiseksi suunnitellut toimenpiteet tulisi ulottaa lapsuusiän lihavuuden ehkäisemiseen. Nopea kasvu ensimmäisinä elinvuosina saattaa olla nuorena aikuisena puhkeavan tyypin 1 diabeteksen riskitekijä.

Tieto nuorten aikuisten diabeteksen ilmaantuvuudesta luo pohjan tuleville epidemiologisille tutkimuksille. Yksityiskohtaisempi tieto tyypin 1 ja tyypin 2 diabeteksen riskitekijöistä auttaa yksilöllisessä riskinarvioinnissa ja voi johtaa patogeneesin mekanismien tarkentumiseen.

Avainsanat: ilmaantuvuus, kasvu, nuoret aikuiset, tyypin 1 diabetes, tyypin 2 diabetes, syntymäjärjestys, syntymäpaino, äidin ikä

Sammanfattning

Niina Lammi. Type 1 and Type 2 Diabetes among Young Adults in Finland. Incedence and Perinatal Exposures. Institutet för hälsa och välfard (THL), Forskning 22. 144 sidor. Helsingfors 2009.
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Diabetes mellitus är ett av de största hoten mot folkhälsan i världen. Tvärtemot vad de tidigare termerna ungdomsdiabetes och vuxendiabetes antyder kan typ 1-diabetes och typ 2-diabetes uppstå vid vilken ålder som helst. Dock är epidemiologin för både typ 1-diabetes och typ 2-diabetes hos finländska unga vuxna inte klarlagd. Dessutom bör riskfaktorerna, som enligt senaste rön har samband med födelsevikten och tillväxten i barndomen, utredas även hos åldersgruppen unga vuxna. Syftet med denna studie är att klarlägga incidensen av typ 1-diabetes och typ 2-diabetes hos finländska unga vuxna samt undersöka eventuella riskfaktorer för diabetes som förekommer under den perinatala perioden och i barndomen.

I de två första delarbeten (I-II) undersöktes incidensen av typ 1-diabetes och typ 2-diabetes hos 15-39-åriga finländare under åren 1992-2001. Uppgifterna om nya diabetesfall inhämtades från standardiserade formulär ifyllda av diabetessköterskor, sjukhusens utskrivningsregister (STAKES, Institutet för hälsa och välfärd), register över läkemedelsersättningar (Folkpensionsanstalten) och register över ersättningsgilla läkemedel (Folkpensionsanstalten). Typen av diabetes fastställdes med hjälp av ovannämnda källor och vid behov fastställdes diabetestypen med hjälp av information i läkarutlåtanden. Resultaten visade att incidensen av typ 1-diabetes hos finländska unga vuxna var 18 per 100 000/år och att av de som insjuknat i typ 1-diabetes var majoriteten män. Under åren 1992-2001 ökade incidensen av typ 1-diabetes i medeltal 3,9 % årligen. Incidensen av typ 2-diabetes hos finländska unga vuxna var 13 per 100 000/år och under tidsperioden för studien ökade incidensen av typ 2-diabetes så mycket som 4,3 % årligen.

I delarbeten III-V undersöktes påverkan av perinatala faktorer och tillväxttid avseende incidensen av typ 1-diabetes och typ 2-diabetes hos unga vuxna genom att använda fall-kontrollstudier. Under tiden 1992-1996 valdes 1388 typ 1-diabetiker och 1121 typ 2-diabetiker som diabetesfall, och för varje diabetesfall valdes två kontrollpersoner ur folkbokföringsregistret matchade för födelsedatum, kön och födelseplats. Data (inklusive födelsedatum) avseende föräldrar och syskon till undersökningspersonerna inhämtades från folkbokföringsregistret. De ursprungliga födelsejournalerna och tillväxtkurvorna från barnavårdscentralen avseende undersökningspersoner inhämtades från arkiven i hela landet. Fall-kontrollstudiernas resultat visade att lägsta risken för att insjukna i typ 2-diabetes som ung vuxen hade

barn till cirka 30-åriga mödrar och risken ökade med moderns fallande eller stigande ålder. Dessutom konstaterades att barn nummer två, tre eller fyra i familjen löpte mindre risk att insjukna i typ 2-diabetes än förstfödda barnet. Risken för typ 2-diabetes hos unga vuxna minskade vid födelsevikten upp till 4,2 kg varefter risken började åter öka. Vid studien av vikten efter födseln visade det sig att högt viktindex vid åldern 3-11 år, då barnets viktindex börjar stiga, väsentligt ökade risken att insjukna i typ 2-diabetes. Hos personer som insjuknade i typ 2-diabetes började övervikten framträda redan i tidiga barnaåren. I motsats till typ 2-diabetes påverkade inte moderns ålder, syskonordning eller födelsevikt för risken att insjukna i typ 1-diabetes hos unga vuxna. Däremot var det maximala viktindexet vid tre års ålder högre hos personer med typ 1-diabetes än hos kontrollpersoner.

Sammanfattningsvis kan konstateras att det är alarmerande att incidensen för både typ 1-diabetes och typ 2-diabetes ökar hos finländska unga vuxna. Inom den finländska befolkningen kvarstår den höga risken att insjukna i typ 1-diabetes åtminstone till 40 års ålder och minst 200-300 finländska unga vuxna insjuknar årligen i typ 2-diabetes. Tillväxten både under fostertiden och i barndomen påverkar väsentligt risken för typ 2-diabetes. För att stävja risken för typ 2-diabetes ska de förebyggande åtgärdena även inkludera barndomsfetma. Snabb tillväxt under de första levnadsåren kan vara en riskfaktor för insjuknande i typ 1-diabetes hos unga vuxna.

Kunskap om diabetesincidens hos unga vuxna lägger grunden för de kommande epidemiologiska studierna. En genomgripande kunskap avseende riskfaktorerna för typ 1-diabetes och typ 2-diabetes är till gagn i den individuella riskbedömningen och kan leda till större förståelse för de patogeniska mekanismerna.

Nyckelord: incidens, tillväxt, unga vuxna, typ 1-diabetes, typ 2-diabetes, syskonordning, födelsevikt, moderns ålder

Contents

List of original publications

This thesis is based on the following original articles referred to in the text by their Roman numerals:

I Lammi N, Taskinen O, Moltchanova E, Notkola I-L, Eriksson JG, Tuomilehto J, Karvonen M. A high incidence of type 1 diabetes and an alarming increase in the incidence of type 2 diabetes among young adults in Finland between 1992-1996. Diabetologia 50(7):1393-400, 2007.

II Lammi N, Blomstedt P, Moltchanova E, Eriksson JG, Tuomilehto J, Karvonen M. Marked temporal increase in the incidence of type 1 and type 2 diabetes among young adults in Finland. Research Letter. Diabetologia 51(5):897-9, 2008.

III Lammi N, Moltchanova E, Blomstedt P, Eriksson JG, Taskinen O, Sarti C, Tuomilehto J, Karvonen M. The effect of birth order and parental age on the risk of type 1 and 2 diabetes among young adults. Diabetologia 50(12):2433-8, 2007.

IV Lammi N, Blomstedt PA, Moltchanova E, Eriksson JG, Tuomilehto J, Karvonen M. Perinatal risk factors in young adult onset type 1 and type 2 diabetes –a population-based case-control study. Acta Obstetricia et Gynecologica Scandinavica. 88(4):468-674, 2009.

V Lammi N, Moltchanova E, Blomstedt PA, Tuomilehto J, Eriksson JG, Karvonen M. Childhood BMI trajectories and the risk of developing young adult-onset diabetes. Diabetologia. 52(3):408-414, 2009.

Abbreviations

ADA	American Diabetes Association
AGA	Appropriate for Gestational Age
AIC	Akaike's Information Criterion
BMI	Body Mass Index
CHD	Coronary Heart Disease
CI	Confidence Interval
C-peptide	Connecting Peptide
DEHKO	Development Programme for the Prevention and Care of Diabetes in Finland
DERI	Diabetes Epidemiology Research International
DIAMOND	Diabetes Mondiale
DOHaD	Developmental Origins of Health and Disease
DPR	Drug Prescription Register
DRR	Drug Reimbursement Register
FPG	Fasting Plasma Glucose
GAD	Glutamic Acid Decarboxylase
GDM	Gestational Diabetes Mellitus
HDR	Hospital Discharge Register
HLA	Human Leucocyte Antigen
IA-2	Protein Thyrosine Phosphatase
IAA	Insulin Autoantibody
ICD	International Classification of Disease
ICP-model	Infancy-Childhood-Puberty-model
IDF	International Diabetes Federation
IGT	Impaired Glucose Tolerance
LADA	Latent Autoimmune Diabetes in Adults
MODY	Maturity Onset Diabetes of the Young
OGTT	Oral Glucose Tolerance Test
OR	Odds Ratio
PI	Ponderal Index
PPAR-γ	Peroxisome Proliferator Activated Receptor – γ
SD	Standard Deviation
SF	Standardized Forms
SGA	Small for Gestational Age
SII	Social Insurance Institute
STAKES	National Research and Development Centre for Welfare and Health
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
WHO	World Health Organization

1 Introduction

Physicians face challenges when diagnosing diabetes among young adults. Type 1 diabetes (T1DM) can be diagnosed at any age (1), and type 2 diabetes (T2DM) is becoming more prevalent among the young (2). Moreover, diabetes first presenting itself in young adulthood may prove to be something in between T1DM and T2DM (3, 4).

Although new cases of T1DM diagnosed among children aged 0-15 years are registered in Finland, there are no registers of T1DM with onset after 15 years of age. In addition, T2DM with onset in adolescence or young adulthood is such a new phenomenon that its magnitude in Finland has not yet been determined. As a first step to understanding the specific characteristics of young adult-onset diabetes among Finns, the incidence of young adult-onset T1DM and T2DM has been examined in this study. It was possible to carry out this study in Finland for several reasons: the Finnish healthcare registers have proven to be comprehensive and highly reliable (5) and therefore they provide a useful tool for tracing new cases of diabetes. In addition, due to the world's highest incidence of childhood-onset T1DM (6) and active educative projects on T2DM (7), Finnish healthcare can also identify these conditions among the more challenging young adult age group.

In addition to basic epidemiology, risk factors for diabetes were also of interest in this study. It was discovered early that a deviation from the adopted growth curve during childhood may be the first sign of disease. Because of this, a close follow-up of growth has been a pertinent part of childhood health surveillance for decades, and the birth weights of newborn babies have been recorded for even longer. Fortunately, the documents including this data have been carefully archived in Finland, as if in anticipation of their new purpose that has been unveiled recently.

The concept of 'Developmental origins of health and disease' (DOHaD), stating that chronic adult diseases result from adaptation to an adverse environment during development, emerged from the observations that body size at birth and childhood growth have a substantial effect on the future risk for T2DM and other chronic diseases (8). It has been shown that individuals born with low (or very high) birth weight (9), who grow slowly during their first years of life (10), and who experience early BMI rebound (11) have an increased risk for T2DM. Moreover, it has also been suggested that early growth has an effect on the risk for childhood-onset T1DM (12). According to studies conducted among individuals with childhood-onset T1DM, individuals with T1DM seem to grow faster than their peers (12, 13). It is not known whether this also applies to cases of T1DM with onset after 15 years

of age. The second part of this study focused on the risk factors for young adult-onset T1DM and T2DM that occur during the perinatal period and childhood.

2 Review of the literature

2.1 Diagnosis and classification of diabetes mellitus

2.1.1 Definition of diabetes mellitus

Diabetes mellitus is defined as a group of metabolic disorders characterized by hyperglycemia. A diagnosis of diabetes is made by measuring the concentration of glucose from a venous plasma sample after 12 h of fasting, or by an oral glucose tolerance test (OGTT, where 75 g of glucose dissolved in water is consumed after 12 h of fasting, and the plasma glucose concentration is measured at 2 h postload). The diagnostic criteria are met when the fasting plasma glucose concentration (FPG) is ≥7.0 mmol/l, or if the 2-h postload glucose is ≥11.1 mmol/l during an OGTT (14, 15) (American Diabetes Association (ADA) and World Health Organization (WHO) criteria). The glucose concentration can also be measured from a venous or capillary whole blood sample, in which case the diagnosis of diabetes is made at the glucose concentration of ≥6.1 mmol/l (fasting value) (16). According to the ADA definition, a diagnosis of diabetes can also be made if any casual plasma glucose measurement is ≥11.1 mmol/l and the person presents classic symptoms of diabetes (15). In Finland, the current diagnostic guidelines follow these international criteria (fasting plasma glucose ≥7 mmol/l, or 2-h postload glucose >11 mmol/l) (17). The current threshold FPG values are from 1997, when ADA tightened the criteria (18) (Table 1).

Table 1. Changes in the diagnostic criteria for diabetes

Organization	Fasting plasma glucose (mmol/l)	2-h postload glucose (mmol/l)
National Diabetes Data Group 1979 (19)	≥7.8	≥11.1
WHO 1985 (20)	≥7.8	≥11.1
WHO 1999-2006 (14, 16)	≥7.0	≥11.1
ADA 1997-2007 (15, 18)	≥7.0	≥11.1

The metabolic disturbances in diabetes mellitus are considerable. The absolute and/or relative insulin deficiency observed in diabetes causes defective glucose uptake in splanchnic and muscle tissues, and the glucose concentration in circulating blood rises. When blood glucose levels rise steadily above normal postprandial values (7-8 mmol/l), part of the excess glucose is excreted in the urine (the renal threshold for glucose is highly variable), and this osmotic diuresis results in the classic symptoms of diabetes: polyuria and polydipsia. Simultaneously, the release of free fatty acids (FFA) from the adipose tissue increases, and these FFAs are then utilized in energy metabolism instead of glucose. Together with glucosuria, this lipolysis results in involuntary weight loss. The inadequate concentration of insulin fails to suppress the secretion of glucagon (a counter-regulatory hormone for insulin), which further exacerbates hyperglycemia by enhancing gluconeogenesis (glucose production) and glycogenolysis (glucose release from the storage form glycogen) in the liver (21).

The acute, severe complications of diabetes mellitus include ketoacidosis and hyperglycemic hyperosmolar states (21, 22). In addition, long-lasting hyperglycemia in poorly controlled diabetes promotes micro- and macroangiopathy, deterioration of the blood vessels, which manifests itself as general arteriosclerosis and cardiovascular disease, nephropathy, neuropathy and retinopathy (15, 23-25). These chronic complications are the major causes of morbidity and mortality associated with diabetes.

2.1.2 Classification of diabetes mellitus

The classification of diabetes mellitus has been under continuous revision (14, 15, 19, 26). The previous classifications of diabetes were based either on age of onset (juvenile vs. adult-onset diabetes), or on the pharmacological treatment (insulin-dependent diabetes mellitus vs. non-insulin-dependent diabetes mellitus) (19). The current ADA and WHO classifications of diabetes (14, 15) are based on the etiology and pathogenesis of diabetes mellitus, as this classification is found to be more appropriate for research purposes (26). Several etiopathogenetic subgroups can be identified among persons with diabetes mellitus.

Type 1 diabetes

In type 1 diabetes (T1DM), which accounts for 5-10% of those with diabetes, hyperglycemia results from an absolute deficiency of insulin caused by the destruction of insulin-secreting pancreatic β-cells (15). The insulinopenia may be evidenced by low or undetectable concentrations of C-peptide (connecting peptide released with insulin in equimolar amounts) (21, 27), and patients with T1DM are dependent on exogenous insulin for survival. T1DM is further subdivided into two

entities: immune-mediated type 1A diabetes, where the destruction of β-cells is caused by an autoimmune process, and idiopathic type 1B diabetes (only the minority of cases) with marked insulinopenia, but no evidence of autoimmunity (15).

The etiology of T1DM is multifactorial. There is a significant genetic predisposition to T1DM, but the mode of inheritance is complex. The most important genes mediating the susceptibility to T1DM are located in the HLA-region of the major histocompatibility complex in the short arm of chromosome 6 (28, 29), where several predisposing and protective haplotypes have been identified. In addition, more than 20 other susceptibility regions have been implicated (28, 30). The T1DM pathogenesis cannot, however, be solely explained by heredity, as the concordance in monozygotic twins is only about 30% (31, 32), and the contribution of susceptibility genes to the incidence of T1DM appears to be decreasing with increasing incidence (33, 34).

The pathogenesis of β-cell destruction in immune-mediated T1DM is intricate. T-cell mediated immunity is considered to be essential in the pathogenesis, and autoreactive T-cells can be detected in the sera of patients with preclinical T1DM (35, 36). As a sign of autoimmunity, islet cell autoantibodies can be detected in the sera of patients with immune-mediated T1DM (islet cells refer to the islets of Langerhans in the pancreas, where the β-cells are situated) (37-39). These islet cell autoantibodies are directed against glutamic acid decarboxylase (GAD, an enzyme present in pancreatic β-cells) (38, 40), and protein tyrosine phosphatase (IA-2) (39) among others. In addition, antibodies to insulin (IAA) (41) have been reported. The occurrence of the autoantibodies in first-degree relatives of T1DM patients has been shown to predict T1DM (42). The current understanding is that unknown environmental factors trigger the autoimmune process leading to T1DM in genetically susceptible individuals.

Type 2 diabetes

Type 2 diabetes (T2DM), which is the most prevalent form of diabetes mellitus with 90-95% of total cases, is characterized by insulin resistance and relative insulin deficiency (15). T2DM can be asymptomatic for several years before diagnosis, and a substantial proportion of patients with T2DM are undiagnosed and consequently without treatment (43, 44).

The risk for T2DM rises with increasing age and is strongly associated with lifestyle factors such as obesity and physical inactivity (all risk factors are discussed in detail below). In individuals with abdominal obesity, the excess visceral adipose tissue promotes insulin resistance through the increased release of free fatty acids, hormones, and cytokines. The increased demand for insulin is exacerbated by the

possible lack of exercise. In the early stages of insulin resistance, pancreatic β-cells can compensate for the increased demand for insulin, but over time, in individuals with susceptibility to T2DM, the β-cells fail to compensate for the insulin resistance resulting in hyperglycemia (45).

However, not all obese individuals develop T2DM. The genetic predisposition for T2DM is strong; the observed concordance rate in monozygotic twins is 50-76% (46, 47). The identification of the susceptibility genes for T2DM has been slow, because multiple genes with relatively modest effect sizes contribute to the individual's risk (48). Candidate gene studies and the recent introduction of new molecular technologies have led to the identification of 11 susceptibility regions influencing the risk for T2DM (49-54). Because the genetic basis for T2DM is now starting to come to light, expectations are high that new information on the molecular pathogenesis of T2DM will be obtained in the near future.

Other types of diabetes mellitus

Besides T1DM and T2DM, the current classification recognizes additional subgroups of diabetes mellitus (14, 15). Gestational diabetes mellitus (GDM) is defined as glucose intolerance first discovered during pregnancy. GDM predicts a future risk for diabetes. Approximately 10% of Finnish women diagnosed with GDM developed diabetes during a 6-year follow-up; half of them developed T1DM and the other half developed T2DM (55). Moreover, the risk of developing T2DM rises to 25% in the next 15 years after the diagnosis of GDM (56). Diabetes mellitus can also be a consequence of genetic syndromes (such as Down's syndrome or Prader-Willi syndrome), diseases of exocrine pancreas (such as pancreatitis), and endocrinopathies. Drugs (e.g. glucocorticoids) or chemicals can also induce diabetes. Maturity onset diabetes of the young (MODY) is a monogenic form of diabetes mellitus caused by single-gene defects affecting β-cell function (abnormalities at six genetic loci have been identified) (15). MODY is inherited in an autosomal dominant pattern and manifests itself at a young age. The prevalence of MODY is unknown, but it is estimated to be a few percent of all patients with diabetes (57).

2.1.3 Characteristics of diabetes in young adults

In addition to the typical cases of T1DM and T2DM, the clinical manifestation of these types of diabetes can overlap substantially in young adults, thus making the classification intricate in this age group. Individuals with T1DM first diagnosed in young adulthood exhibit higher C-peptide values at diagnosis (27, 58, 59), slower disease progression (59, 60), and less high-risk genotypes (59-61) than children with a prepubertal diagnosis of T1DM. On the other hand, individuals with early-onset

T2DM can have characteristics of T1DM, as a considerable number of individuals diagnosed to have T2DM in adolescence have been demonstrated to be positive for islet autoantibodies (30% GAD positive and 35% IAA positive) (62). In the UK Prospective Diabetes Study, the percentage of patients with T2DM presenting GAD autoantibodies was negatively correlated with age at onset (34% in 24-35-year-olds vs. 7% in 55-60-year-olds) (63), and positive autoantibodies strongly predicted the need for insulin therapy during a 6-year follow-up period. A marked loss of β-cell function has also been associated with early-onset T2DM (64).

2.1.4 Intermediate type of diabetes

Considering the overlap between the two major types of diabetes, it seems that a third type of diabetes, an intermediate type between T1DM and T2DM, may exist. Patients who are obese and insulin resistant with simultaneous markers of autoimmunity are often referred to as having the intermediate type of diabetes (3, 4, 65), but this group is heterogeneous in its characteristics. Several names have been suggested for this intermediate type, such as type 1.5 diabetes (66) and double diabetes (4, 65), but the designation that has gained ground most is 'latent autoimmune diabetes in adults' (LADA) (67-70). Adult age at onset (>35 years), presence of circulating GAD antibodies, and absence of a requirement for insulin at diagnosis have been suggested as the criteria for LADA (68). However, the basis of this classification has been criticized (71), and it has been proposed that autoimmune diabetes is more of a continuum with T1DM and LADA at opposite ends rather than two separate entities (71, 72). In addition, the authors of a review summarizing clinical characteristics of LADA state that the epidemiological studies concerning LADA have produced conflicting results and propose that the continuum of diabetes types may also include T2DM (69). The latest clinical guidelines consistently direct physicians to treat diabetes according to clinical manifestation, and to put less emphasis on the assigned type of diabetes (17).

Consensus criteria that would unequivocally separate the intermediate type or LADA from atypical phenotypes of T1DM or T2DM have not been defined. It has been suggested that instead of etiology, the future classification of diabetes should put emphasis on the common disease mechanisms leading to hyperglycemia (73).

2.2 Epidemiology of diabetes mellitus

The ultimate goal of epidemiological research is to find causes that can explain disease occurrence (74). Thus, before examining the etiology of diabetes, the occurrence of diabetes must be examined. The occurrence of T1DM is commonly reported as the incidence rate (the occurrence of new cases per unit of person-time (74)), whereas the prevalence (the proportion of people in the population at risk who have the disease at a specific time (74)) is more often reported in studies of T2DM.

2.2.1 Epidemiology of type 1 diabetes in children

T1DM constitutes 5-10% of all cases of diabetes, and it is one of the most common chronic non-communicable diseases in children (21). The majority of knowledge on the epidemiology of T1DM is provided by studies investigating cases with onset before the age of 15 years. In the 1980s, the first international collaboration was initiated in order to obtain standardized data on the incidence of T1DM in children. The Diabetes Epidemiology Research International (DERI) was the first group to establish standardized population-based registries allowing comparison of the incidence of T1DM between countries (75). The DERI was followed by the EURODIAB ACE project, designed to investigate the variation of T1DM incidence in Europe (76, 77), and in 1990 WHO launched the Diabetes Mondiale (DIAMOND) project to expand this surveillance worldwide (6, 78). These large studies reported a remarkable geographical variation in the incidence levels of T1DM. The variation in incidence was over tenfold between the European populations in 1989-1998. The lowest incidence was observed in Macedonia (3.6 per 100,000/year), and the highest incidence in Finland (43.9 per 100,000/year) (77). Globally, the variation in incidence exceeded 350-fold, when comparing Finland with China (0.1 per 100,000/year) during 1990-1999 (6). The studies investigating the geographical distribution of T1DM have consistently reported that the variation in incidence follows the distribution of ethnic groups; the highest rates of T1DM have been recorded in Europids (6, 79) and the lowest rates in the Asian populations (6, 78). Moreover, considerable intra-country variation has also been reported in genetically homogenous populations (80-82). Despite the efforts of the EURODIAB ACE and the DIAMOND projects, the incidence of T1DM remains unknown in many developing countries.

According to the EURODIAB ACE and the DIAMOND studies, the incidence of T1DM was the lowest in the age group of 0-4-year-olds and thereafter increased with age reaching twofold incidence rates in 10-14-year-olds (6, 76). There were no significant differences in the incidence between genders (6).

The incidence of T1DM in children is increasing rapidly (6, 77, 83). In Europe, the average annual increase in the incidence during 1989-1998 was 3.2% (77), and the worldwide annual increase was 3.0% during 1960-1996 (83). In the DIAMOND study, the strongest increase in the incidence of T1DM was observed across areas with high or intermediate incidence (6). The increase was more rapid in the age group of 0-4-year-olds than in the older age groups (6, 77). Unfortunately, the standardized collection of data on the incidence of T1DM was discontinued within the framework of the DIAMOND study after 1999, which is why new information on worldwide incidence trends cannot be expected in the near future.

The rapid rise in the incidence levels is considered to be one of the strongest arguments in favor of the environmental etiology of T1DM, because the increase is far too fast to be caused only by the natural selection of genes. However, in addition to the triggering environmental exposures, epigenetic factors may be one potential explanation for the increasing incidence of T1DM.

In order to identify clues leading to possible environmental risk factors, the seasonality of the diagnosis of T1DM has been widely investigated. In several populations, lower incidence rates have been observed in the summer months (77, 84, 85), but analogy, for example to the seasonal patterns of microbial infections, has not been confirmed (84, 85). It also seems that the seasonality of the diagnosis of T1DM may vary depending on the age at diagnosis (77, 84). A recent study based on worldwide DIAMOND data showed that the existence of a significant seasonal pattern correlated with a higher level of incidence (86).

In Finland, the incidence of childhood-onset T1DM is increasing more rapidly than the worldwide average (87-89). The incidence was rising on average 3.4% annually between 1965-1996 (87) and even faster, on average 4.1% annually, between 1992-2005 (90). From 1997 to 2001, the incidence of T1DM in 0-14-year-old Finns was 49.1 per 100,000/year (91), and there was a slight male predominance with a male/female ratio of 1.08 (92).

2.2.2 Epidemiology of type 1 diabetes in adolescents and young adults

Compared to the registers of childhood-onset T1DM, the collection of information on the incidence of T1DM in the population aged 15 years or older is less well organized and restricted to short observation periods. The incidence of T1DM in young adults is more difficult to estimate than in children, because other types of diabetes (T2DM, GDM, MODY, and secondary forms of diabetes) exist in young adults concomitantly, and a misclassification of the type of diabetes may occur especially when hyperglycemia is first diagnosed. In addition, as the onset of T1DM

in adults is often less acute than in children, all new cases are not necessarily hospitalized and might not end up in registers. Due to these difficulties, the case-ascertainment rate in the studies on the incidence of T1DM in young adults is considerably lower than in studies on children, making comparison difficult.

The studies investigating adolescent- and young adult-onset T1DM are reviewed in Table 2. In persons aged 15-19 years, the incidence of T1DM generally seems to be lower than in children (93, 94) and decreasing with age thereafter (93, 95-97). It is noteworthy that several studies on childhood-onset T1DM including the age group of 15-19 show that the peak in the incidence is during puberty (79, 82, 98-100), between 10 and 14 years, whereas in the post-pubertal age groups incidence is lower. The peak in the incidence of T1DM occurs earlier in females than in males following the timing of maturation (82, 101). The geographical variation in the incidence of T1DM among young adults is narrower than among children, and it seems that the decrease in incidence after the age of 15 is steeper in the high incidence areas, thus equalizing the incidence levels (102).

Estimating the annual trend in T1DM incidence in young adults is challenging, because most of the studies cover only short periods. However, contrary to the increasing trend in childhood-onset T1DM, it has been suggested that the incidence after the age of 15 would remain stable (97, 103). Whilst marked sex differences in the incidence do not exist in children (6, 77), in adolescents and young adults, unexplained male predominance has been reported (82, 93, 94, 96, 97, 104, 105). In addition, there are few studies on the incidence of T1DM in young adults from the USA (98, 106) that report male excess in incidence similar to the European studies. Female excess has only been reported in New Zealand (107).

The incidence of T1DM in Finnish adolescents was studied three decades ago between 1970-1979, when the incidence of T1DM in the age group of 15-19 years was found to be 24.1 per 100,000/year (82).

Table 2. Studies investigating the incidence of type 1 diabetes among young adults (Studies including individuals aged 15-29 years arranged by latitude)

Authors	Study area	Age at dg	Years	Incidence/100,000/year (95% CI)	M/F ratio	Ascert. rate (%)
Joner et al (104)	Norway	15-29	1978-1982	17.0	na	87.8
Blohme et al (96)	Sweden	15-34	1983-1987	na	1.8	86
Thunander et al (108)	Kronoberg (Sweden)	10-19 20-29 30-39	1998-2001	29.4 (28.0-32.1) 19.7 (18.0-21.7) 11.7 (10.4-13.2)	na	100
Christau et al (101)	Denmark	15-29	1970-1974	12.8	na	na
Ostrauskas et al (109)	Lithuania	15-39	1991-1997	7.8 (7.3-8.4)	1.8	91
Vandewalle et al (105)	Antwerp (Belgium)	15-39	1989-1995	8.9 (7.8-10.2)	1.7	85
Roglic et al (95)	Zagreb (Croatia)	15-24 25-34	1988-1992	9.6 (7.1-12.7) 6.5 (4.8-8.6)	na	93-100
Bruno et al (93)	Turin (Italy)	15-29	1984-1988	5.8 (4.9-6.9)	1.8	93
Allen et al (98)	Dane La Crosse (Wisconsin, USA)	15-29	1970-1979	10.6 11.1	na	75
Goday et al (97)	Catalonia (Spain)	15-29	1987-1990	9.9 (9.8-10.8)	na	90.1
Muntoni et al (94)	Sardinia (Italy)	15-29	1989-1990	18.8 (15.9-21.7)	na	92.4
Kadiki et al (110)	Benghazi (Libya)	15-34	1981-1990	11.9 (10.3-13.8)	na	>95

na= not available

2.2.3 Epidemiology of type 2 diabetes

An overview of the prevalence of T2DM can be obtained from studies investigating the prevalence of all types of diabetes, as T2DM accounts for more than 90% of diabetes cases in most populations (21). The total amount of individuals with diabetes was assessed to be 246 million in 2007 (2), and an estimated 960,000 deaths were caused by diabetes in 2001 (111). Moreover, the prevalence of T2DM is increasing rapidly (2, 112), and it has been predicted that the number of people with diabetes will rise to 380 million by 2025 (2).

The worldwide T2DM epidemic is caused by the global transition from traditional to modern lifestyles, which often results in obesity and physical inactivity (113-115). In addition, demographic changes such as population growth, increase in life expectancy, and urbanization increase the number of diabetic subjects further (2, 112). Taking into account the varying genetic susceptibility and the degree of changes in lifestyle between populations, it is evident that some populations are more severely affected than others. The estimated prevalence of diabetes for the year 2000 in the population ≥20 years of age was 6.3% in developed countries (Europe, North America, Japan, Australia, and New Zealand), and 4.1% in developing countries (all others), and the predictions for the year 2030 were 8.4% and 6.0% respectively (116). In 2000, the highest prevalence of T2DM (>10% in the populations ≥20 years) was estimated to be in Greece, Malta, Qatar, the Arab Emirates, Nauru, Singapore, Mauritius, and Seychelles (116), whereas the countries having the highest number of cases were India, China and the USA (112). Among the ethnic groups that have undergone a prominent transition in lifestyle, extremely high prevalence rates have been reported: nearly 50% among 30-64-year-old Pima and Papago Indians of Arizona and 40% among Micronesian Nauruans (117). The profound effect of lifestyle transition is clear, as the prevalence of T2DM was observed to be less than one-fifth in the Mexican Pima Indians compared to the U.S. Pima Indians, whose common ancestry was proved by DNA testing (118). The lowest prevalence rates of T2DM are found in the rural areas of the least developed countries (2, 117).

In developing countries, diabetes affects younger age groups than in developed countries, where the greatest increase in the prevalence is expected in the population over 65 years of age (112). The risk for T2DM and its major risk factor, obesity, are strongly linked to poverty and lower socio-economical status also in developing countries (113, 114, 119). The greatest increase in the prevalence of T2DM is estimated to occur in India, where the number of diabetic patients could reach 80 million by 2030 (112).

The male/female (M/F) ratio in the prevalence of T2DM varies markedly among individual communities (117). In the younger age groups there is a slight male predominance, but in the older age groups there is a female excess (2, 112). Globally, the number of women with diabetes is greater due to their higher life expectancy.

In a cross-sectional population-based survey conducted during 2004-2005, the prevalence of T2DM among 45-74-year-old Finns was 16% in women and 11% in men (120), which makes T2DM one of the most important public health problems in Finland.

2.2.4 Type 2 diabetes among children and adolescents

Even though the first report of pediatric patients with T2DM appeared in 1979 (121), T2DM was rare in children and adolescents before the 1990s (122). When cases of T2DM first started to appear in children and adolescents, the problem was assumed to only concern ethnic minority groups on the North American continent. However, it was soon perceived that youth-onset T2DM was a worldwide phenomenon (2, 123-128). Although the epidemiological data on T2DM in children and adolescents is still very limited, it has been recognized that concomitantly with the rising prevalence of youth overweight, the incidence of early-onset T2DM is increasing (2, 122, 129, 130). The only report of a decreasing trend in the 21st century has been from Tokyo (131), where the prevalence of obesity also simultaneously decreased. The studies investigating the incidence of childhood and adolescent-onset T2DM are reviewed in Table 3.

Ethnicity plays a significant role in the risk for T2DM with early onset, as the highest risk for childhood-onset T2DM is borne by indigenous populations (130). Youth-onset T2DM seems to be more prevalent in females than in males (132), which may be partially explained by the increasingly prevalent polycystic ovarian syndrome predisposing to T2DM (122). Young age does not protect patients with T2DM from complications, and early-onset T2DM can lead to morbidity or even mortality during the productive years of life (127). For example microalbuminuria (the earliest sign of diabetic nephropathy) has been reported to be more frequent in adolescents with T2DM than in those with T1DM (133).

Table 3. Studies investigating the incidence of type 2 diabetes among children and adolescents (arranged by study period)

Authors	Study area	Age at dg	Study years	Incidence/100,000/year (95% CI)	M/F ratio	Ascert. rate (%)
Lipton et al. (134)	Hispanic and African-American population of Chicago (the USA)	0-17	1985-1994	3.2 (2.7-3.8)	na	83-86
Urakami et al. (126)	Tokyo (Japan)	6-12 13-15	1974-2002	0.8 6.4	0.6 0.9	100
Thunander et al. (108)	Kronoberg (Sweden)	0-9 10-19	1998-2001	0 5.6 (4.9-6.9)	na	100
Dabalea et al. (128)	6.2% of population aged 0-19 in the USA	0-4 5-9 10-14 15-19	2002-2003	0 (0.0-0.2) 0.8 (0.5-1.2) 8.1 (7.1-9.2) 11.8 (10.5-13.2)	0.6	93

na=not available

Adolescent overweight has also been rapidly increasing in Finland. In 1977, the prevalence of overweight and obesity in Finnish adolescents aged 12-18 years was 7.2% in males and 4.0% in females, but by 2003 the corresponding percentages were 19% and 12% (135, 136). Moreover, the cardio-respiratory fitness of Finnish conscripts, as measured by the results of a 12-min running test, decreased by 12% (1979-2004) (137), and the prevalence of metabolic syndrome among Finnish 24-year-old individuals increased from 1.0% in 1986 to 7.5% in 2001 (138). The number of Finnish adolescents and young adults with T2DM is unknown.

After the recognition of the imminent T2DM epidemic among young individuals, both the International Diabetes Federation (IDF) and ADA have published consensus statements (130, 139) that urgently demand more research on the epidemiology, treatment, prevention, and outcome of youth-onset T2DM.

2.3 Risk factors for diabetes mellitus

The confirmed and suggested risk factors for diabetes mellitus by clinical type are summarized in Table 4.

Table 4. Risk factors for T1DM and T2DM

	T1DM	T2DM
Confirmed risk factors	Genetic predisposition Young age	Genetic predisposition Old age Obesity, overweight, and central obesity
Possible risk factors with evidence from at least three epidemiological studies	Micobial infections Microbial toxins Vitamin D deficiency (142) High intake of nitrosamine-rich food (143) Early introduction of cow's milk High maternal age Caesarean section High birth weight Fast growth during childhood	High intake of saturated fat (140) Low intake of dietary fibre (141) Lack of exercise Cigarette smoking (144) Decreased sleep duration (145) Low socio-economic status Birth size and early adiposity rebound Bottle feeding in infancy Low ground water magnesium (146)

Risk factors without reference are discussed and cited in the main text.

In T1DM, the autoimmune process leading to the destruction of the pancreatic β-cells is affected by environmental factors operating either as a trigger or an accelerator in the process. Several possible mediators, such as rate of growth in infancy (147), early nutrition (148), antenatal factors (149), viral infections (150), and bacterial toxins (151) among others (Table 4) have been proposed. However, a final consensus regarding their role in the pathogenesis of T1DM has not been reached thus far.

Unlike the risk factors for T1DM, the concomitant occurrence of T2DM with obesity (body mass index (BMI) >30 kg/m^2) is well documented (152, 153). Moreover, the location of the excess adipose tissue is of importance. Visceral fat accumulation has been shown to cause a higher risk for T2DM than subcutaneous adipose tissue (152), as the risk for T2DM rises with increasing waist circumference in individuals with a similar BMI (154). Among others (Table 4), a sedentary lifestyle has been suggested to be a risk factor for T2DM independent of obesity (155). In addition to lifestyle factors, the effects of fetal and childhood growth on the risk for T2DM have attracted increasing interest during the last 15 years (156).

The risk factors behind adult-onset T2DM seem to also apply to childhood- and adolescent-onset T2DM. There is evidence that a family history of T2DM, obesity, abdominal deposition of body fat, physical inactivity, and the effects of fetal growth are the main contributors (2, 122, 157).

The possible risk factors for T1DM and T2DM related to the perinatal period, infancy, and childhood are reviewed in detail below.

2.4 Early life risk factors for diabetes mellitus

The onsets of both T1DM and T2DM are typically preceded by long subclinical periods, and it is therefore reasonable to search for possible causative environmental factors from many years before diagnosis. A vast number of epidemiological studies have aimed to find associations between perinatal conditions and the risk for diabetes.

2.4.1 Parental attributes influencing the risk for type 1 diabetes

Parental socio-economic status may contain potential non-genetic risk factors for T1DM, as it has a profound effect on many prenatal exposures such as health behaviors, living conditions, and nutrition. However, the association between socio-economic status and the risk for T1DM remains unsettled. Both increased (158, 159) and decreased (160-162) incidence of T1DM have been associated with a higher socio-economic status, while the majority of studies report that there is no variation in incidence attributable to wealth (163-168). The conflicting results may be explained by the diverse definitions and classifications of socio-economic status examined in these studies, which vary from parental education to the gross domestic product of the country.

Several studies have shown that the risk for childhood-onset T1DM rises with increasing maternal age (165, 168-173). It has been suggested that factors related to high maternal age may influence the maturation of the immune system in the child (169), thus predisposing the child to T1DM. In addition, advanced maternal age increases the occurrence of hypertension during pregnancy, pre-eclampsia, gestational diabetes, and delivery by Caesarean section (174), which may indirectly modify the risk for T1DM. The reported elevations in the risk have been modest, 12-13% per every 5-year increase in maternal age (168, 169).

The effect of maternal age may vary according to the characteristics of the population. A British study including patients from the Oxfordshire area found no association between maternal age and the risk for T1DM (175), whereas a study

comparing two British areas only reported an association in Scotland, but not in Northern Ireland (176). In addition, studies with a more specific stratification of the study population have revealed that the effect of high maternal age may be uneven between different subgroups. The effect of maternal age may vary according to the sex of the offspring (177), birth order (149), or age at the diagnosis of T1DM (166). Most of the studies investigating the effect of maternal age have only included patients under the age of 16 at the time of diagnosis of T1DM. The only study also including individuals with young-adult onset T1DM found no association between maternal age and the risk for T1DM (178).

While maternal age at delivery is normally documented in birth records, data on paternal age at conception is more difficult to obtain. The risk for selection bias is high, as in population-based datasets paternal age is more often missing for firstborn children, for children of younger mothers, and in lower socio-economical classes (169). In the Northern Ireland cohort, the risk for T1DM increased with advancing paternal age (169), whilst a large Norwegian study did not find this association (149).

In addition to the age of the parents, the birth order of the child (i.e. parity of the mother) in relation to the risk for T1DM has also been of interest. Although most studies have taken the correlation between maternal age and birth order into account, the results have been conflicting. Several studies have not found any association between birth order and the risk for T1DM (166, 175, 178, 179). However, there are also studies reporting contradicting results of a decreasing (168-170) or increasing (172) risk for T1DM with increasing birth order. The complex interactions between maternal age and birth order may explain these conflicting results: in a population-based cohort study, a decreasing risk for T1DM with increasing birth order was detected only among children of mothers aged under 30 (149).

Caesarean section has also been reported to increase the individual's risk for T1DM (165, 166, 176, 180). An increased rate of Caesarean sections in mothers with T1DM could explain this association, but the effect remained statistically significant in the studies that were controlled for maternal T1DM (165, 180). It has been suggested that the quality of the bacteria first encountered by the newborn (180) or the non-specific stress experienced during birth by Caesarean section (166) may explain this association. However, evidence of an increased risk attributed to Caesarean sections has not been found in all studies (172), and an increased risk for T1DM related to complicated vaginal delivery instead of a Caesarean section has also been reported (181). Other less studied possible risk factors for T1DM are mother-child blood group incompatibility (166, 172) and pre-eclampsia (165, 166, 175), both of which may be associated with the maturation of the immune system in the offspring.

2.4.2 Parental risk factors for type 2 diabetes

Low socio-economic status predisposes to T2DM (119), which is explained to a large extent by the variation in nutrition, physical activity, and other related health behaviors between socio-economic groups (119, 182). The increased risk for T2DM seems to be mediated mostly through increased adiposity (183) in deprived individuals.

The effects of parental age and parity on the risk for T2DM have been only little studied. It is well acknowledged that the prevalence of gestational diabetes increases with advancing maternal age (174), and evidence is accumulating that gestational diabetes in the mother may increase the risk for T2DM in the offspring independently of genetic factors (184). In addition, parity of the mother influences some key perinatal exposures such as birth weight (185, 186) and would therefore be worth examining. A study conducted in the 1990s suggests that birth order after fourth may be a risk factor for T2DM (187), while a cohort-study examining the associations between birth weight, adult adiposity and perinatal exposures found no association between parity and the risk for T2DM (183).

2.5 Fetal and childhood growth and the risk for diabetes

2.5.1 General concepts of childhood growth

The infancy, childhood, puberty (ICP)-model
The vertical growth of an individual begins from conception and ends when the growth plates of the long bones close due to the effect of sex hormones in the end of puberty. According to Karlberg, childhood growth consists of three components: infancy, childhood, and puberty, which reflect the three different hormonal phases of the growth process, and can each be described by separate mathematical functions (ICP-model presented in Figure 1) (188).

Fetal growth in utero is dependent on the genetic growth potential of the fetus, the placental supply of oxygen and nutrients, the maternal nutritional status, and several hormones of which insulin and insulin-like growth factors are the most critical (189). According to the ICP-model, the infancy growth period comprises both fetal growth and its postnatal continuation. This rapid growth period continues until the age of 1 year, decelerating thereafter, and ceasing at the age of 3-4 years (188).

Simultaneously with the infancy growth period, the childhood growth period begins at approximately 1 year of age and continues slowing down gradually until the individual is full-grown (188). The most important promoter for childhood growth is the normal secretion of the growth hormone that regulates the insulin-like growth hormone system postnatally. In addition to the growth hormone, adequate secretion of the thyroid hormone is a prerequisite for normal postnatal growth, while insulin is also an important regulator (190).

The increasing activity of the gonads sets off the third growth period during puberty, when sex steroids initiate the final pubertal growth spurt before the same hormones cause the growth plates to close, thereby ending vertical growth (188). This period occurs earlier in females than in males, following the timing of maturation. The pubertal growth spurt overlaps with the end phase of the childhood growth period.

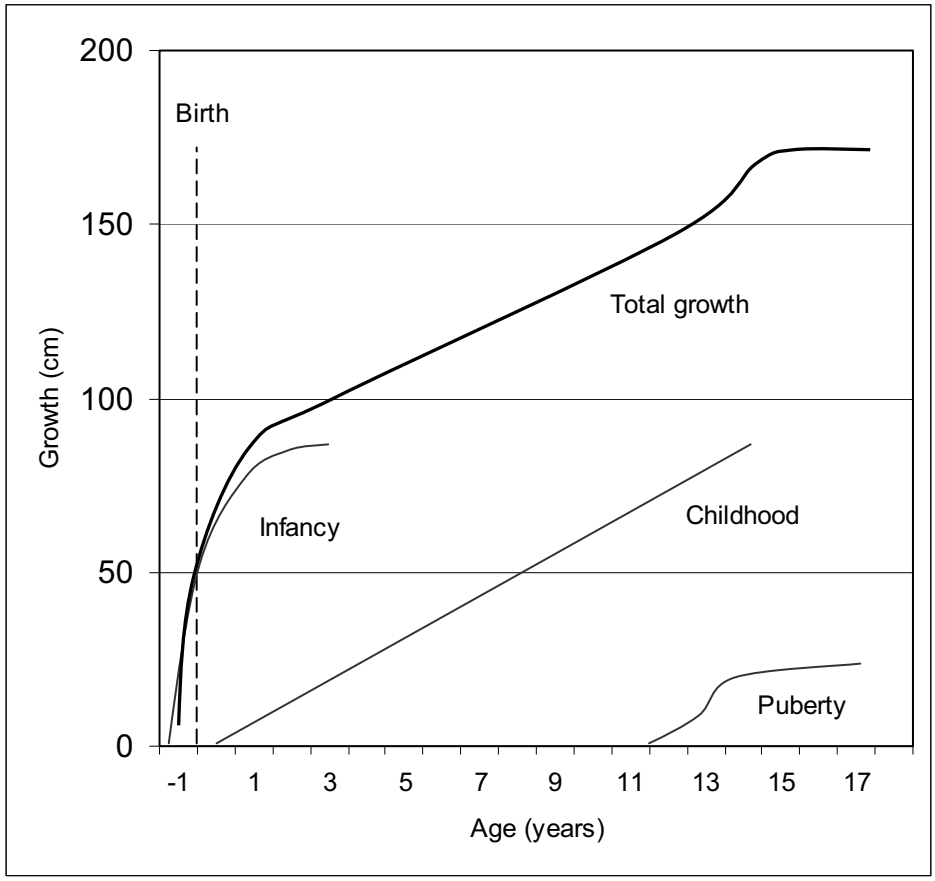


Figure 1. Three components of childhood growth according to Karlberg (188)

Anthropometric measurements in newborns and children

During 1979-1983, the mean birth weight of Finnish males born at term (40 weeks of gestation) was 3,722 g and their mean length was 51.1 cm. The same values for females were 3,582 g and 50.2 cm respectively (191). The higher birth weight among male newborns is suggested to result from anabolic effects of testosterone, and the differences in birth weights between sexes are shown to be consistent across all ethnic groups (192). Birth weight generally increases with parity and is lowest in the firstborn child (185).

Body mass index (BMI) is defined as body weight (in kilograms) divided by the square of height (in meters). While the BMI thresholds of normal weight for adults (18.5-25 kg/m^2) (193) cannot be applied to children, BMI-for-age has been proven useful in predicting overweight also in the 2-19-year-old population (194). While the vertical growth of a child is always positive with advancing age, the BMI growth curve also adopts negative values, because it is dependent on the changing body proportions during growth. The BMI of a newborn typically varies from 12 to 16 kg/m^2. After the neonatal period, the BMI of a child normally increases reaching its peak at the age of 1-2 years. After that, the BMI starts to decrease, followed by the BMI rebound (the point at which the BMI begins to increase again) typically between ages 3-8 years (193). The normal BMI growth curve is illustrated in Figure 2.

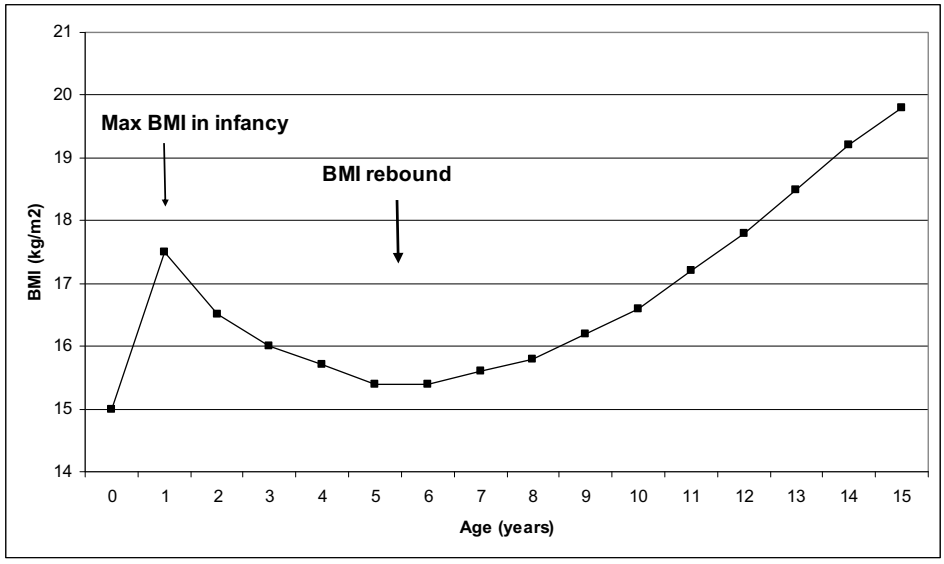


Figure 2. Change in BMI during growth. Average BMI values adopted from Centers for Disease Control and Prevention (195)

The ponderal index (PI, defined as the cube root of body weight times 100 divided by height in cm) is comparable to BMI in the evaluation of the relationship between weight and height, but it enables a more fair comparison of infants and children of different stature, which is why it is often used instead of BMI when evaluating children at birth (196).

2.5.2 Fetal and childhood growth and the risk for type 1 diabetes

In 2001, Wilkin introduced 'the Accelerator hypothesis' (197) proposing that T1DM and T2DM are essentially the same disorder and the difference between them is only in the tempo of β-cell loss. According to the hypothesis, three accelerators operate to a different extent in individuals who will later develop diabetes: an intrinsic high rate of beta-cell apoptosis, insulin resistance, and beta-cell autoimmunity. The rapid weight gain among western populations especially increases the prevalence of insulin resistance, which according to the hypothesis, is the environmental factor causing the increasing incidence of both T1DM and T2DM. Closely related is 'the Overload hypothesis', stating that the overfeeding of children leads to accelerated growth that overloads beta-cells thereby causing an increased risk for T1DM (198).

The association between body size and the risk for T1DM has already interested researchers before the introduction of the Accelerator hypothesis. Several studies have provided evidence that high birth weight may be a risk factor for T1DM (168, 169, 172, 199, 200). In a Norwegian population-based cohort, the association between the incidence of T1DM and birth weight was almost linear (200). An elevated risk for T1DM with high birth weight has also been reported from Australia (168), and the UK (169), and a pooled analysis combining data from seven European areas found low birth weight to be protective from T1DM (172). However, there are several studies that report no association between the incidence of T1DM and birth weight (147, 167, 175, 201-203), birth length (167, 202), or ponderal index at birth (167). A study including individuals with both childhood-onset and young adult-onset T1DM reported a significant association between high birth weight and the risk for T1DM only among those who were diagnosed before 10 years of age, and not among the later-onset cases (204).

The mechanisms by which birth weight may modify the risk for T1DM are unknown. To make the matter more complex, it was recently reported that the required dose of insulin was in fact lower in children with T1DM born with high birth weight, and the authors suggested that birth weight may be a determinant of insulin resistance in T1DM (205). Moreover, children diagnosed with T1DM between the ages 0-4 years weighed significantly less at birth than those who developed diabetes later (147). On the other hand, it has been shown that the HLA

genotypes predisposing to T1DM are associated with rapid intrauterine growth resulting in high birth weight (206, 207).

Most of the studies assessing an association between gestational age and the risk for T1DM have found no such association (175, 178, 200). A decreasing risk with increasing gestational age has been reported (168, 169), and one study found a small risk elevation in those born before 38 weeks of gestation (166). There are also reports of an increased risk in individuals born large for their gestational age (178, 199), but this has not been confirmed in all studies (175).

Although no conclusion on the role of birth weight or gestational age in the etiology of T1DM has been made, there is strong evidence indicating that individuals who develop T1DM grow faster than their peers during infancy (12, 13, 147, 208, 209). In the 1990s, it was observed that the weight gain from birth to 6-30 months of age was greater in children subsequently developing T1DM (147), and boys were taller prior to the diagnosis than their age-matched controls (208). Subsequently, a Finnish case-control study reported that children diagnosed with T1DM were heavier and taller than their controls throughout childhood (12). This finding was also later confirmed (13, 209). All these studies were conducted among individuals who were younger than 15 years of age when diagnosed with T1DM.

The fast growth among children with T1DM may be caused either by genetic factors or infant nutrition. A reduced risk for T1DM among breastfed children has been observed (13, 210). Moreover, it has also been reported that breastfed children gain less weight than bottle fed children, and it has been suggested that this may explain the protective effect of breastfeeding (147). On the other hand, bottle feeding with cow's milk formula may be a risk factor independently of childhood growth, as the increased risk for T1DM in children with early bottle feeding remained after adjustment for their individual weight gain curves (201).

In support of the Accelerator hypothesis, it has been reported that the BMI of an individual and the age of onset of T1DM are inversely correlated (211-214), but all studies have not been able to confirm this correlation (215, 216). Estimating the possible associations between BMI and T1DM onset is difficult, however, as involuntary weight loss is one of the major symptoms of T1DM. The only study also including individuals with young adult-onset T1DM found no association between an individual's BMI and age of T1DM onset (217). Although there is some evidence supporting the Accelerator hypothesis, it has remained controversial (218).

2.5.3 Risk factors for type 2 diabetes related to fetal growth and growth during infancy

Twenty years ago, Barker and his colleagues showed in a Hertfordshire cohort that mortality from coronary heart disease (CHD) fell with increasing birth weight (219). This observation led to the formation of 'the fetal origins of adult disease hypothesis', stating that chronic adult diseases result from fetal adaptation to an adverse environment during development (220). It was discovered later that the plastic phase of development is not restricted to the fetal period, and the hypothesis was expanded to 'the developmental origins of health and disease (DOHaD)' concept (8), with wide-ranging consequences on our knowledge of the early origins of chronic non-communicable diseases.

The observation that CHD was associated with conditions in utero was rapidly applied to other related adult diseases. In 1991, Hales and Barker reported that the odds ratio to develop impaired glucose tolerance (IGT) or T2DM was 6.6 for men whose birth weight was ≤2.5 kg compared to those weighing >4.3 kg at birth (221). In addition, an inverse association between birth weight and the risk for metabolic syndrome was demonstrated in a cohort of 266 individuals from Preston by the same authors (222). Subsequently, the increased risk for T2DM in low birth weight individuals was confirmed in the USA (223, 224), Sweden (225, 226), and Finland (227) among others (228-230).

However, a study conducted among Pima Indians in the USA indicated that the relationship between birth weight and a subsequent risk for IGT and T2DM was not linear but U-shaped (231). In this study, maternal diabetes during pregnancy was associated with an increased risk for IGT and T2DM among individuals with birth weight ≥4.5 kg. A similar relationship between birth weight and the risk for T2DM was observed among Taiwanese schoolchildren (232). Two recent reviews that have examined the relationship between birth weight and T2DM support these observations: the possible positive association at high birth weights could not be ruled out in the analysis by Whincup and colleagues (233), and the analysis by Harder and associates showed a U-shaped pattern (9).

The risk for T2DM was also found to be associated with anthropometric measurements other than birth weight. As a marker of reduced fetal growth, both short birth length (227) and a low ponderal index (225, 227) have been reported to increase the risk for T2DM. In South India, an increased risk for T2DM was found among individuals with high ponderal indices and heavy mothers (234), representing the elevated risk in the macrosomic babies of glucose-intolerant mothers.

When an association between a possible exposure and subsequent disease is found by epidemiological methods, the first concern is to determine whether it is caused by confounding factors. Birth weight is to a large extent influenced by the length of gestation. Many studies examining the association between birth weight and the risk for T2DM did not record gestational age (221, 223, 229, 235), but those who controlled for gestational age did not find significant changes in results compared with crude birth weights (224, 236). Two studies reported that gestational age was not associated with the risk for T2DM (227, 232), while one study found a slight increase in the risk for T2DM for preterm babies (228). It has also been debated whether the studies examining the effect of birth weight should be adjusted for adult BMI (237). Lucas and colleagues even argue that some reported associations between birth size and T2DM may result from careless adjustment for suspected confounding factors such as current body size (238). For example, an analysis aiming to explore the association between birth size and T2DM is actually exploring the effect of change in body size from birth to the present if the analysis is adjusted for current body size. In addition, birth size often correlates with current body size, which has to be taken into account when interpreting results. In most studies that have adjusted for adult body size, the risk elevation in low birth weight individuals has been independent of adult BMI (221, 223, 231) or waist circumference (229). An adverse adult or childhood environment represented by low socio-economic status does not seem to explain the risk conveyed by intrauterine growth retardation either (221, 227).

Early studies investigating the association between early growth and T2DM already found an increased risk for T2DM in individuals who had low weight at 1 year of age (221). Additional information on the effect of childhood growth was provided by studies examining two cohorts born in Helsinki (10, 11, 227, 239). These studies showed that the risk for T2DM was greatest in those who were small at birth (227), grew slowly until the age of 2 years (10), experienced an early adiposity rebound (11), and experienced accelerated growth between the ages of 7-15 years (227). A large, prospectively followed cohort from South Delhi confirmed the results of the Helsinki cohort (236), and it was consistently reported from the UK that an early adiposity rebound (235) and rapid growth of the BMI in adolescence (230) increased the risk for T2DM.

The most important environmental determinant of early infant growth is appropriate nutrition. A systematic review of studies investigating the effect of breastfeeding on the risk for T2DM suggested a reduced risk for breastfed children compared to those who received formula (240).

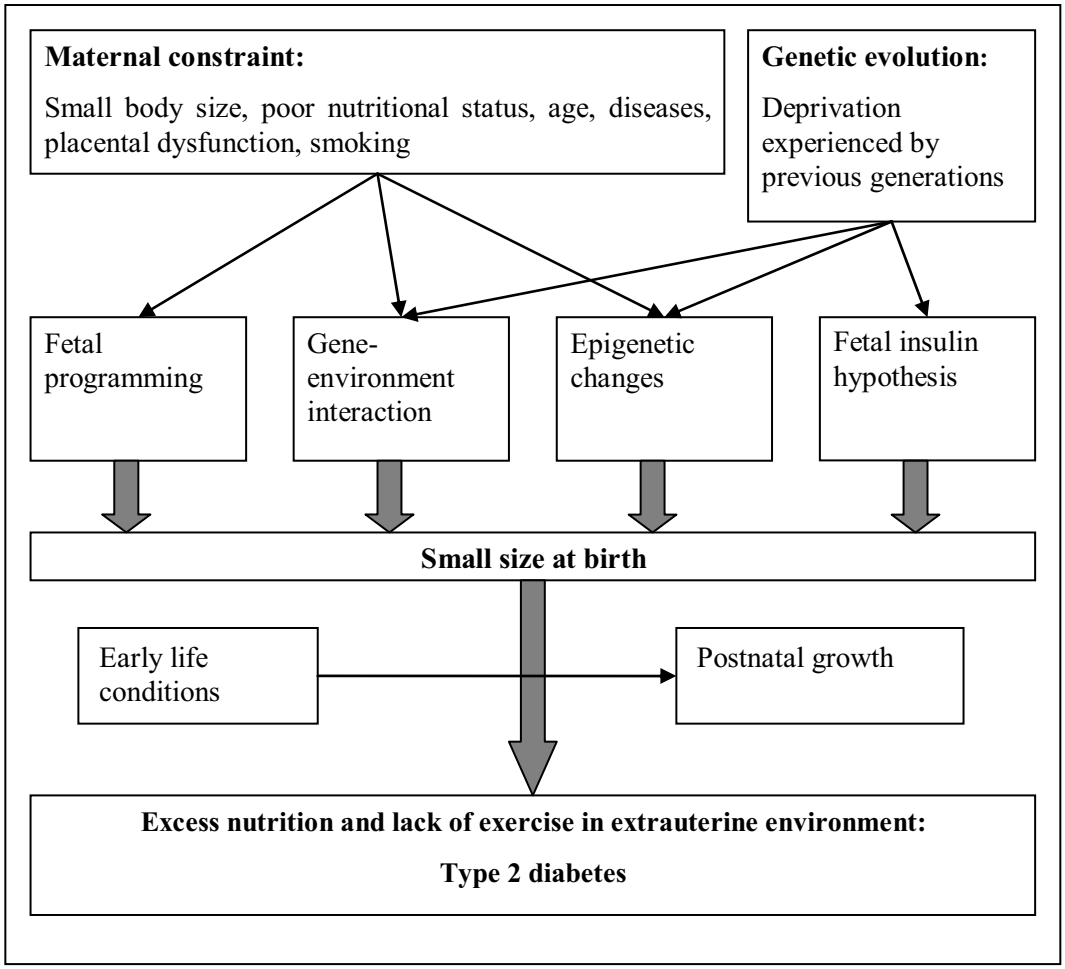


Figure 3. Suggested mechanisms for the association between birth size and type 2 diabetes

The observed association between low birth weight and the risk for T2DM has elicited several explanations (Figure 3). The fetal origins hypothesis (220) suggests that in response to inadequate oxygen and nutrient supply in utero, the fetus undergoes metabolic adaptations, such as enhanced glucose supply to the vital organs at the expense of the muscle tissue, thereby improving survival. As a result, the fetus fails to achieve the birth weight determined by its genetic growth potential. However, once the plastic period of development is over, these adaptive changes cannot be reversed. Therefore, individuals who are permanently adapted to an efficient utilization of the available nutrition will have an increased susceptibility to obesity, insulin resistance, and CHD in an affluent adult environment. However, recent findings based on experiments on laboratory animals suggest that

reprogramming may be possible during the late phase of developmental plasticity. In rat offspring with low birth weight, leptin treatment during the postnatal days 3-13 reversed the metabolic changes caused by the malnutrition in utero (241).

It is likely that growth trajectories during the fetal and early postnatal periods merely reflect the underlying adaptation process (fetal programming) and do not cause adult disease itself. Evidence from the Dutch famine showed that the incidence of CHD was highest in individuals whose mothers had been exposed to famine during early gestation, and this effect was independent of birth weight (242). It has also been reported that low birth weight and slow BMI growth during the first two years of life predict lower lean mass and a higher body fat percentage in adulthood (243, 244), thereby increasing the risk for T2DM independently of the absolute attained BMI. A tendency to a sedentary lifestyle may also be programmed prenatally: an experiment with rats showed that low birth weight offspring of undernourished rats were significantly less active than those born with normal birth weight (245).

In addition to the concept of fetal programming, it has been suggested that the association between low birth weight and susceptibility to T2DM is caused by a genetic predisposition to both of them. 'The fetal insulin hypothesis' states that genetically determined insulin resistance in the fetus causes impaired insulin-mediated growth in utero, resulting in low birth weight and an increased risk for T2DM in adulthood (246). Additionally, it has been suggested that birth weight is lower than average among offspring of diabetic fathers (247), and there is evidence that susceptibility alleles for T2DM may affect birth weight (248). However, the fetal insulin hypothesis does not explain for example the results of the Helsinki Study of Very Low Birth Weight Adults (249), which showed that among young adults born prematurely with a birth weight of less than 1,500 g, there were no differences in insulin resistance between individuals born small for gestational age (SGA) and individuals born appropriate for gestational age (AGA). Instead, when compared to young adults born at term with normal birth weight, young adults (both SGA and AGA) who were born at less than 1,500 g were significantly more insulin resistant.

There is increasing evidence that epigenetic changes (changes in gene expression that are stable between cell divisions, but do not involve changes in the underlying DNA sequence) may have a role in the early programming of adult disease. One of the mechanisms of epigenetic modification is DNA methylation, which affects the regulation of gene expression. Wolff and his colleagues reported a link between maternal diet, DNA methylation, and the phenotype of the offspring in mice: feeding a methyl-supplemented diet to pregnant mice altered the epigenetic gene regulation and phenotype in their offspring (250).

It is also possible that gene-environment interactions play a role in determining an individual's risk for T2DM (251). It has been reported that the association between small body size at birth and insulin resistance was apparent only among individuals who were carriers of the high-risk allele of the PPAR-γ gene (52, 252), indicating that the effect of genotype was modified by intrauterine growth retardation.

While several possible mechanisms behind the association between low birth weight and T2DM are still being considered, expectations are high that a more profound understanding of the underlying mechanisms leading to T2DM will provide new means for primary prevention. However, while fetal and childhood growth may have a marked effect on the future risk for T2DM, the importance of lifestyle factors in the pathogenesis of T2DM should not be underestimated. Regardless of the conditions during the fetal period and early infancy, the risk for T2DM can be substantially reduced by lifestyle interventions among high risk individuals (253).

3 Aims of the study

The aims of the study were to examine the incidence of T1DM and T2DM among young Finnish adults aged 15-39 years, and to determine the effects of prenatal and infancy exposures on the risk for young adult-onset T1DM and T2DM.

The specific aims of the study were:

- To determine the ten-year (1992-2001) incidence of T1DM and T2DM among young Finnish adults with special emphasis on the annual variation in incidence (Papers I-II).

- To study the effects of perinatal exposures such as parental age, birth order, birth weight, gestational age, placental weight, and maternal body size on the risk for young adult-onset T1DM and T2DM (Papers III-IV).

- To assess the effect of BMI growth trajectories on the risk for young adult-onset T1DM and T2DM (Paper V).

4 Materials and methods

4.1 Study subjects

Papers I-II

Information on new diagnoses of diabetes was collected among people aged 15-39 years who were resident in Finland and diagnosed between January 1st 1992 and December 31st 2001. Data for this register-based study were obtained from four different sources:

1. During the years 1992-1996, new cases of diabetes were reported to the Diabetes and Genetic Epidemiology Unit of the National Public Health Institute using standardized forms (later SF) filled in by diabetes nurses in hospitals and primary care diabetic clinics in Finland. The date of diagnosis of diabetes and the date of the start of insulin treatment were included in the forms.

2. The Finnish National Hospital Discharge Register (HDR), maintained by the National Research and Development Centre for Welfare and Health (STAKES), includes up to four hospital discharge diagnoses of patients who have been admitted to a hospital ward. The treating physicians assign the diagnostic codes using the International Classification of Diseases (ICD-9 until 1995 and ICD-10 from 1996 onwards). The Finnish version of ICD-9 also includes information about the type of diabetes (see Appendix 1 for the codes). The diagnoses made in hospitals were based on clinical characteristics, C-peptide measurements and, in part of the cases, glutamic acid decarboxylase (GAD) antibody measurements.

3. Since late 1994, all Finnish prescriptions have been included in the Drug Prescription Register (DPR) of the Social Insurance Institute (SII). Prescriptions searched for were all the class A10 drugs in the WHO Anatomical-Therapeutic-Chemical Classification System (drugs used in diabetes; insulin and analogues, blood glucose lowering drugs, other drugs used in diabetes) (254).

4. The Drug Reimbursement Register (DRR) of the Social Insurance Institute comprises information on persons entitled to free-of-charge medication for diabetes. Glucose-lowering agents (insulin and oral

medication) prescribed by a physician are free-of-charge in Finland and are subject to the approval of a physician of the Social Insurance Institute, who reviews each case history. Patients who apply for free-of-charge medication must attach a detailed medical statement prepared by the treating physician, who provides data to confirm the diagnosis of diabetes. Individuals with T2DM are only entitled to free-of-charge medication after a 6 month period of lifestyle intervention, which is why these medical statements also include details about the type of diabetes, clinical characteristics, and treatment. However, the DRR records only include information on the diagnosis of diabetes, but not the type of diabetes. Individuals with GDM are not entitled to free-of-charge medication unless the need for glucose-lowering medication continues after delivery.

The data obtained from registries were linked using the unique personal identification number assigned to every Finnish resident. The date of diagnosis was set as the date of the first entry in one of the registers.

All individuals who had any diabetes-related information from at least two data sources were included in the data at the beginning of the study. Cases with apparent gestational diabetes and secondary forms of diabetes were then excluded from the data if they fulfilled the following criteria:

- Gestational diabetes: female sex, only diagnoses of GDM in the HDR (ICD-codes 6480A, 6488A, O24.4, and O24.9), no entitlement to free-of-charge medication, no purchases of oral glucose-lowering agents

- Diabetes secondary to other diseases: diagnosis of certain genetic syndromes, diseases of exocrine pancreas, or endocrinopathies prior to the diagnosis of diabetes mellitus in the HDR (ICD-codes: 5770, 5771, 5779, 0723A, 157, 2530A, 2550A, 2750, 2751, 2770A, 5710-5713, 7517A, 7580A, 8680A, 2513A, K85, K86, K86.3, K87.1, K90.3, B26.3, C25, E22.0, E24, E31.00, E83.1, E83.0, E84. K70, Q45.0-Q45.3, Q90, S36.2, and E89.1)

The remaining cases were classified as T1DM, T2DM or an undefined type of diabetes. The classification criterion was a consistent diagnosis from at least two data sources. The information from the four data sources was used in the classification as follows:

- First insulin administration on the day of diagnosis (while not pregnant) according to the standardized form was counted as a reference to T1DM.

- Diagnoses with ICD-codes 2500B-2508B, E10.0-E10.9, and O24.0 in the HDR were counted as a reference to T1DM.

- Insulin administration immediately at the diagnosis and continued until the end of the available information on the DPR (the end of the year 2004) was counted as a reference to T1DM.

- Diagnoses 2500A-2508A, E11.0-E11.9, and O24.1 in the HDR were counted as a reference to T2DM.

- Only temporary entitlement to free-of-charge medication was counted as one source referring to T2DM, because in T1DM permanent entitlement is admitted at the diagnosis.

- Treatment with only oral glucose-lowering agents was counted as a reference to T2DM.

- Diagnoses 2500C, 2500X, E12, E13, E14, G59.0, G63.2, G73.0, G99.0, H28.0, H36.0, I79.2, M14.6, N08.3, O24.2, O24.3, P70, and R73 did not allow conclusions as to the type of diabetes.

- When insulin was first administered years after the diagnosis, this information did not allow conclusions as to the type of diabetes, as the onset of T1DM may be slow in young adults and T2DM may require insulin during the natural course of the disease.

Cases with equivocal information on the type of diabetes (no two sources consistently referring to T1DM or T2DM) were further scrutinized. For these individuals, the original applications for free-of-charge medication were obtained from the SII (n=1,428). The records were reviewed by a physician (N.L.). Based on the clinical characteristics and treatment reported in the applications, the type of diabetes was assigned according to the 2006 criteria of ADA (255). Information available on the unclear cases who had not applied for free-of-charge medication was reviewed and classified. Most of these cases were found to have gestational diabetes (diagnosis of childbirth in the HDR within 6 months of the record referring to diabetes, and no further records in the HDR or in the DPR) and they were excluded from the study.

A total of 8,547 cases were jointly ascertained from the four data sources. Women diagnosed with GDM (n=1,702) and patients with secondary forms of diabetes (n=347) were excluded. The remaining (6,491) cases were classified as T1DM (n=3,078), T2DM (n=2,392), and undefined diabetes (n=1,021). The group

of undefined diabetes cases included individuals with confirmed or suspected MODY or LADA and all individuals with inadequate information for classification. Data sources and classification are illustrated in Figure 4.

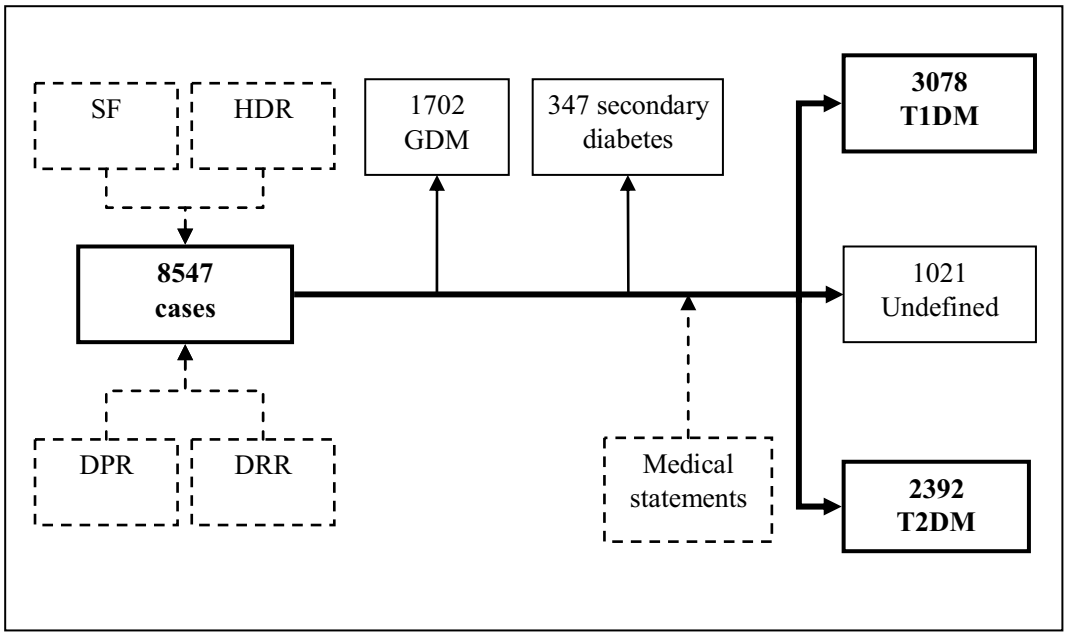


Figure 4. Data sources and classification of the diabetes mellitus cases.
SF= Standardized forms, HDR= Hospital Discharge Register, DPR= Drug Prescription Register, DRR= Drug Reimbursement Register

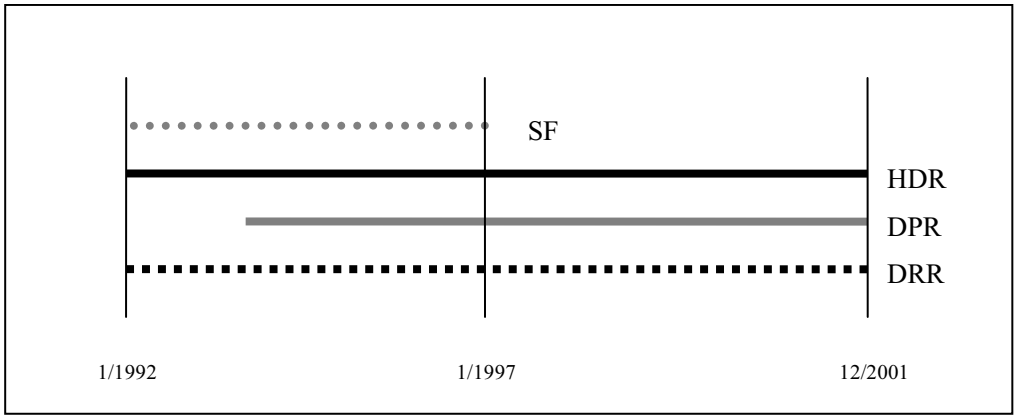


Figure 5. Coverage of the data sources relative to the study period

Case ascertainment

The capture-recapture method (256), often used in the assessment of the case-ascertainment rate in register-based diabetes research, was not completely applicable to this study. A prerequisite for the capture-recapture method is that the data sources used need to be independent. In this study, the DPR, the DRR, and the HDR were not independent sources. Moreover, the coverage of these data sources was uneven (as illustrated in Figure 5). The second independent data source, SF, was only available for the first half of the study period. Standardized forms were efficient in detecting individuals with T2DM treated only with lifestyle intervention, as these individuals are not registered in the DPR or the DRR. Therefore, it can be assumed that the case-ascertainment rate was higher between the years 1992-1996 than between 1997-2001. When calculated with the capture-recapture method using the standardized forms as the primary data source and other sources combined as the secondary data source, the case-ascertainment rate between 1992-1996 was 88% for T1DM, T2DM, and undefined diabetes together (annual variation 88%-90%). Due to the lack of two independent data sources, it was not possible to calculate the case-ascertainment rate for the years 1997-2001, but for the above mentioned reasons, it is likely to be somewhat lower.

Papers III-V

A case-control setting was formed in order to examine the associations between perinatal exposures, childhood growth and the risk for young adult-onset diabetes reported in papers III-V.

Individuals with T1DM (n=1,388) and T2DM (n=1,121) diagnosed during 1992-1996 (the first half of the study period), were chosen as the diabetes cases for the case-control study. Individuals with GDM, secondary diabetes, and undefined diabetes were excluded.

Two non-diabetic control individuals matched by birth date, birth place, and sex were randomly chosen from the National Population Register for each diabetic subject. For 33 subjects with T1DM and 34 subjects with T2DM, only one control was found. The non-diabetic status of the control individuals was confirmed by computer linkage to the HDR, the DPR and the DRR.

Data on the parents and the siblings of the study subjects, including their dates of birth, were obtained from the National Population Register.

4.2 Data on perinatal exposures and childhood growth

Papers IV-V

Birth records and child welfare clinic records were collected for cases and controls from hospital and health center archives and the archives of municipalities nationwide. The records were traced based on information on the place of birth, which was obtained from the National Population Register.

Finnish birth records are filed under the name and birth date/personal identification number of the mother in the hospital where the delivery took place. In order to find the birth records, names and personal identification numbers of the mothers were obtained from the National Population Register. Because there was no specific information on the hospital where the study subject was born, birth records were searched from all hospitals (university, central and district hospitals) located in the same province as the municipality of birth. The birth records include information on maternal health during pregnancy, course of delivery, gestational age, and size of the newborn.

The health and development of Finnish children aged 0-7 years are monitored in child welfare clinics, where children are taken to regular examinations performed by public health nurses and primary care physicians. From the age of 7 onwards these examinations are conducted by school healthcare until the end of compulsory education at age 15. An essential part of this follow-up is the measurement of the height and weight of the children, which are documented in the child welfare clinic records. These records also include information on the duration of breastfeeding, the body size and health of the child as a newborn, and socioeconomic factors during childhood. These records are filed in the archives of the healthcare center or in the archives of the municipality where the child was living when finishing school. As there was no information available on the possible relocation to a different municipality, the child welfare clinic records were only searched from the municipality and healthcare center of the place of birth. The records were inquired after from the 200 largest Finnish municipalities (with a population of over 3,500), either from the archives of the healthcare center or the municipality, depending on the practices of the municipality in question.

Altogether 4,440 child welfare clinic records and 3,812 birth records were obtained. The birth weight measurements in birth records and child welfare clinic records were compared for persons for whom both were available. The recorded birth weight differed between the two sources by less than 100 g in 96.8% of the records and was identical in 93.4% of them.

4.3 Ethical aspects

The study plan was approved by the National Advisory Board on Health Care Ethics. Birth records and child welfare clinic records were reviewed with the permission of the Ministry of Social Affairs and Health.

4.4 Statistical methods

All statistical analyses were performed using R-software (257). A p-value of <0.05 was considered to be statistically significant.

Papers I-II

The incidence of T1DM, T2DM, and undefined diabetes were analyzed separately. Sex- and age-specific incidence was calculated for 5-year age groups (15-19, 20-24, 25-29, 30-34, and 35-39 years). Age-standardized annual incidence rates were calculated using WHO standard European population, where the age groups in question are identical in size. The observed cases were assumed to result from a Poisson distribution, and the exact 95% confidence intervals (CI) were approximated as described by Anderson et al. (258). The male-female (MF) ratio was calculated by age group for each diabetes type, and the corresponding 95% CI was evaluated as previously described (74). The effects of age, gender, and year of diagnosis were assessed using a generalized linear model for the Poisson family with a logarithmic link.

Paper III

Maternal age was analyzed both as a continuous and a categorical variable, and the mode for maternal age (25.5 years) was chosen as the baseline. Data on case-control pairs of T1DM and T2DM were analyzed separately. The effects of maternal age on the risk for both types of diabetes were analyzed using conditional logistic regression (259). A quadratic term was added to the model, as it displayed a better fit than a linear model, as measured by Akaike's information criterion (AIC) (260). Categorical birth order was adjusted for maternal age. Birth orders 6 through 12 were pooled into one category because of their low frequency in the data. The frequency of maternal age >44 years was also low, but this group was decided to be examined separately. It was tested that pooling maternal ages 40-44 and >44 together would not have changed the results. The effect of birth order on the risk for diabetes was analyzed using conditional logistic regression. To test the interaction between birth order and maternal age, an interaction term was initially included in the model. This was, however, not found to be significant in either type of diabetes.

Paper IV

The effects of birth weight and other perinatal exposures on the risk for diabetes were analyzed using conditional logistic regression. For birth weight, three different models were estimated: linear, quadratic and piecewise linear (261) with a single break point. The fits of the three models were compared using AIC. For the piecewise linear model, the location giving the best fit was chosen as the break point. Furthermore, a 95% basic bootstrapped confidence interval for the break point was estimated (262). Models including a quadratic term were also estimated for height, placental weight and gestational age, but a better model fit in terms of AIC was achieved with only linear terms. For each of the other variables (BMI and ponderal index at birth and maternal anthropometric measurements), only a linear model was estimated.

Paper V

Conditional logistic regression was used to evaluate the effect of the properties of individual BMI growth curves on the risk of developing T1DM or T2DM. In order to define the properties of the BMI growth curves, the ICP-model for human growth (188) was used as a starting point. This model breaks down growth into three additive components: infancy (0-3 years), childhood (3-11 years), and puberty (>11 years), each component being a separate parametric function of age (the mathematical functions are described in (188)). Only the first two components were considered in the analyses due to the scarcity of measurements after 11 years of age. The parameters were first estimated using the least squares errors criteria. From each individual growth curve a set of characteristics were extracted to be used as explanatory variables in conditional logistic regression. The extracted characteristics were as follows:

- the maximum BMI value in the infancy component
- the age at which the maximum BMI value in the infancy component is reached
- the minimum BMI value in the childhood component (the BMI rebound)
- the age at which the minimum BMI value in the childhood component is reached.

The results were adjusted for birth weight. For most individuals, the estimation of the infancy component was not possible due to too much variation in the BMI values between ages 0-2 years. Therefore, observed instead of estimated values were extracted from this component.

The effect of breastfeeding on the risk for T1DM and T2DM was also examined using conditional logistic regression.

5 Results

5.1 Diabetes incidence and trends in young adults (aged 15-39 years) in Finland during 1992-2001

Papers I-II

After excluding cases of GDM and secondary forms of diabetes, the total number of young Finnish adults diagnosed with diabetes during 1992-2001 was 6,491. Of these, 47.4% (3,078/6,491) were classified as having T1DM, 36.9% (2,392/6,491) as having T2DM, and for 15.7% (1,021/6,491) the type of diabetes remained undefined. The incidence rates according to the type of diabetes, sex, and age at diagnosis are shown in Table 5. The incidence rates are presented per 100,000/year.

The overall age-adjusted incidence of T1DM was 18.0 (95% CI 17.4-18.6), being 22.4 (21.4-23.4) for men and 13.4 (12.6-14.2) for women. A significant male predominance in the incidence of T1DM was found across all examined age groups. The incidence was highest in the youngest 5-year age group (15-19 years) and decreased with increasing age. During the study period, the incidence of T1DM increased on average by 3.9% (2.7-5.3) per year ($p<0.001$) (Figure 6).

The total age-adjusted incidence of T2DM was 12.9 (12.4-13.5). In both men and women, there was a considerable increase in the incidence after the age of 30. The highest incidence, 43.2 (40.3-46.2), was observed in men aged 35-39. In this age group, there was also a significant male predominance. During the study period, the incidence of T2DM increased on average by 4.3% (3.0-5.9) per year ($p<0.001$) (Figure 6).

The incidence of undefined diabetes was 5.7 (5.3-6.0). The number of cases with undefined diabetes increased with age. The incidence of undefined diabetes remained stable during 1992-2001.

Table 5. Incidence of T1DM, T2DM and undefined types of diabetes in Finland during 1992-2001

		Men			Women			Total			M/F ratio	
	Age group (years)	Cases (n)	Incidence /100,000/y	95% CI	Cases (n)	Incidence /100,000/y	95% CI	Cases (n)	Incidence /100,000/y	95% CI	Ratio	95% CI
T1DM	15-19	509	30.4	27.8-33.2	272	17.0	15.0-19.1	781	23.9	22.2-25.6	1.8	1.41-2.27
	20-24	357	22.0	19.8-24.4	202	13.0	11.3-15.0	559	17.6	16.2-19.2	1.7	1.28-2.24
	25-29	409	24.0	21.7-26.5	221	13.6	11.8-15.5	630	18.9	17.5-20.4	1.8	1.36-2.31
	30-34	388	20.6	18.6-22.8	234	13.0	11.4-14.8	622	16.9	15.6-18.3	1.6	1.22-2.07
	35-39	288	14.7	13.1-16.5	198	10.5	9.1-12.1	486	12.6	11.5-13.8	1.4	1.04-1.88
	All age-adjusted	1951	22.4	21.4-23.4	1127	13.4	12.6-14.2	3078	18.0	17.4-18.6	1.7	
T2DM	15-19	8	0.5	0.2-0.9	16	1.0	0.6-1.6	24	0.7	0.5-1.1	0.5	0.11-1.93
	20-24	37	2.3	1.6-3.1	47	3.0	2.2-4.0	84	2.7	2.1-3.3	0.8	0.37-1.54
	25-29	98	5.8	4.7-7.0	154	9.4	8.0-11.1	252	7.6	6.7-8.6	0.6	0.40-0.92
	30-34	402	21.4	19.3-23.6	311	17.3	15.4-19.3	713	19.4	18.0-20.8	1.2	0.97-1.58
	35-39	846	43.2	40.3-46.2	473	25.1	22.9-27.5	1319	34.3	32.5-36.2	1.7	1.44-2.06
	All age-adjusted	1391	14.6	13.9-15.4	1001	11.2	10.5-11.9	2392	12.9	12.4-13.5	1.3	
Undef. Diabetes	15-19	38	2.3	1.6-3.1	26	1.6	1.1-2.4	64	2.0	1.5-2.5	1.4	0.61-3.25
	20-24	37	2.3	1.6-3.1	52	3.4	2.5-4.4	89	2.8	2.3-3.5	0.7	0.34-1.36
	25-29	78	4.6	3.6-5.7	93	5.7	4.6-7.0	171	5.1	4.4-6.0	0.8	0.49-1.32
	30-34	155	8.2	7.0-9.7	132	7.3	6.1-8.7	287	7.8	6.9-8.7	1.1	0.77-1.65
	35-39	273	13.9	12.3-15.7	137	7.3	6.1-8.6	410	10.7	9.7-11.8	1.9	1.38-2.68
	All age-adjusted	581	6.3	5.8-6.8	440	5.1	4.6-5.6	1021	5.7	5.3-6.0	1.2	

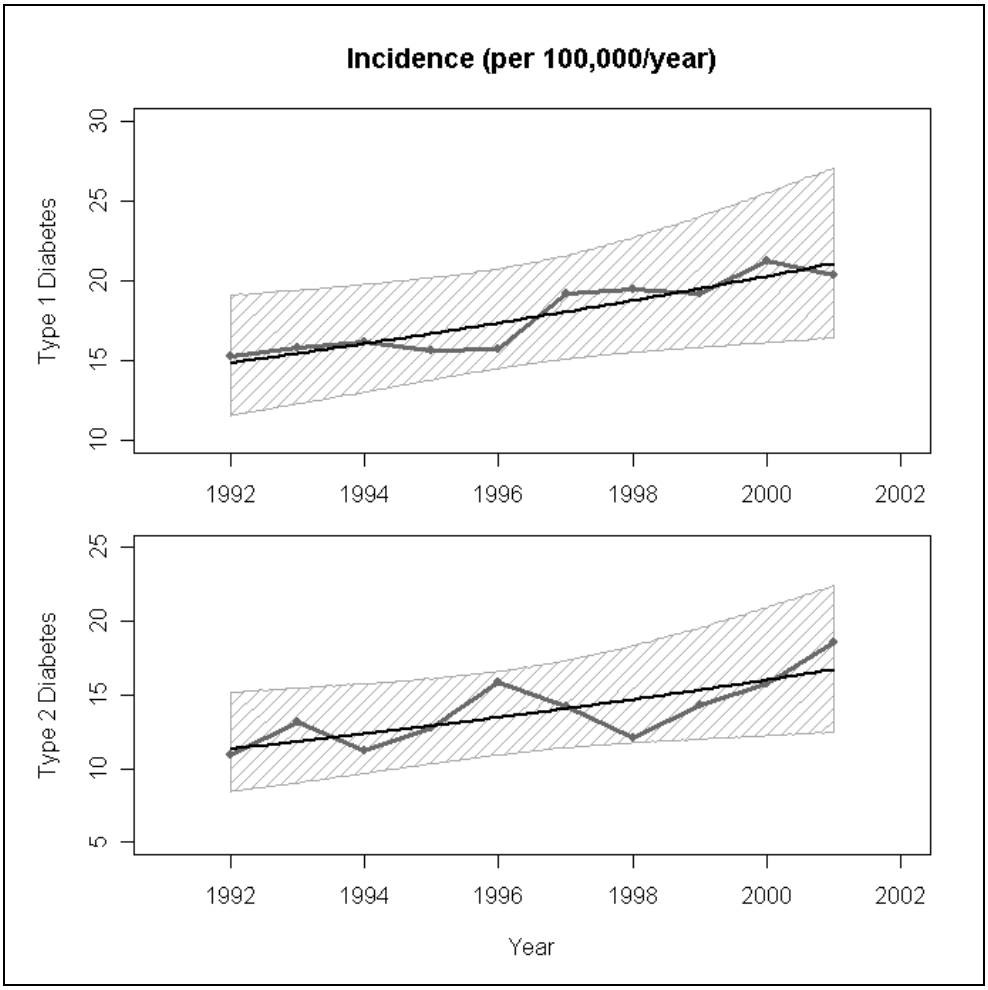


Figure 6. Observed and estimated incidence trends for T1DM and T2DM in 15-39-year-old Finns.
Observed incidence (dots), estimated trend (straight line), 95% confidence intervals (shaded area).

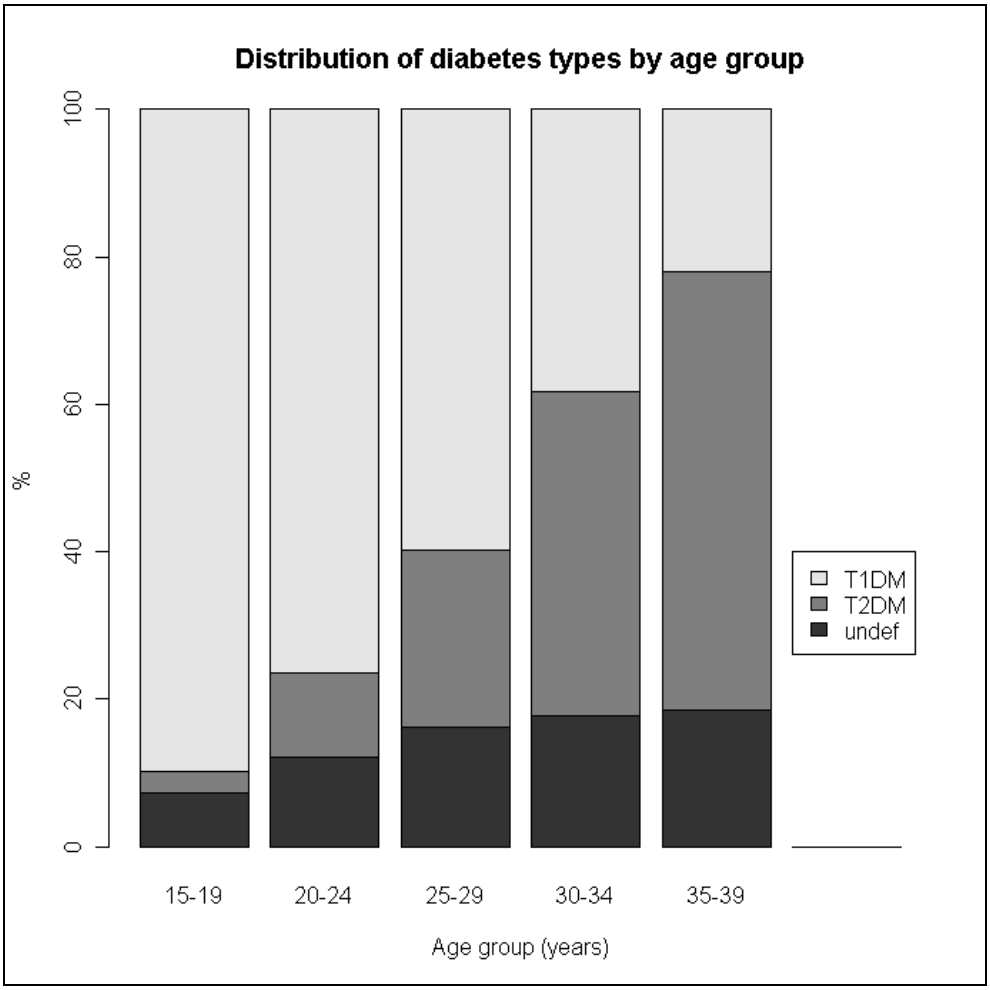


Figure 7. Distribution of diabetes types by age group (%)

In the youngest age group of 15-19 years, 91% of all new cases of diabetes were of T1DM, whilst the proportion of cases with verifiable T2DM was only 3% (Figure 7). After the age of 30 years, the proportion of cases with T1DM decreased to less than half of the new cases, and in the age group of 34-39 years, the share of T2DM was already 60%.

5.2 The effect of parental age and birth order on the risk for young adult-onset T1DM and T2DM

Paper III

All the case-control pairs for whom data on parents and siblings was available in the National Population Register (for the case and at least one of the controls) were included in the analyses. This resulted in the inclusion of 1,345 case-control pairs of T1DM and 1,072 case-control pairs of T2DM in the analysis of parental age, and 1,272 pairs of T1DM and 943 pairs of T2DM in the analysis of birth order. (The original number of case-control pairs was 1,388 of T1DM and 1,121 of T2DM.)

Maternal age was highly correlated with paternal age (correlation coefficient, ρ=0.8) and therefore analysis was carried out using maternal age alone. The odds ratios (ORs), describing the effect size between the examined exposure and outcome, for T1DM and T2DM by maternal age and birth order adjusted for maternal age are presented in Table 6.

Results of the conditional logistic regression showed that maternal age categorized into 5-year age groups or birth order adjusted for maternal age did not have any effect on the risk for young adult-onset T1DM (Table 6). The quadratic model for T1DM, where maternal age was treated as a continuous variable, also proved non-significant (Figure 8a).

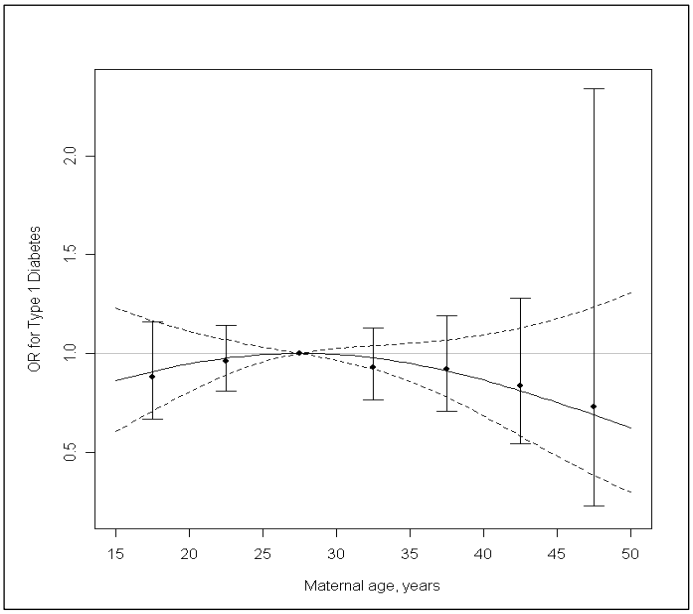
Instead, both maternal age and birth order adjusted for maternal age influenced the risk for young adult-onset T2DM in the offspring. Second [OR 0.76 (95%CI 0.62-0.94)], third [OR 0.73 (0.55-0.95)], and fourth-born children [OR 0.66 (0.47-0.94)] had a significantly lower risk for T2DM than the firstborn child ($p<0.05$) (Table 6). When maternal age was categorized into 5-year age groups, maternal age did not have a significant effect on the risk for T2DM in the offspring (Table 6). However, the categorical model suggested a U-shaped pattern for the effect. Therefore, a logistic regression model with a quadratic term was applied, where maternal age was treated as a continuous variable. The results of the quadratic model showed that compared to the mode maternal age of 25.5 years, the risk for T2DM was lowest in the offspring of mothers aged around 30 years, whereas the risk for T2DM increased towards younger and older maternal ages. (Figure 8b). The p-values were 0.02 for both the linear and the quadratic terms.

Table 6. Odds ratios (ORs) for T1DM and T2DM by maternal age and birth order adjusted for maternal age

	T1DM				T2DM			
Maternal age	**Cases (n)**	**Controls (n)**	**OR**	**95% CI**	**Cases (n)**	**Controls (n)**	**OR**	**95% CI**
15-19	95	201	0.88	(0.67-1.16)	75	125	1.28	(0.93-1.78)
20-24	406	803	0.96	(0.81-1.41)	330	626	1.16	(0.95-1.42)
25-29	431	824	1.00		273	602	1.00	
30-34	237	486	0.93	(0.77-1.13)	185	385	1.08	(0.86-1.36)
35-39	112	229	0.92	(0.71-1.19)	114	206	1.24	(0.94-1.64)
40-44	34	74	0.83	(0.54-1.28)	50	91	1.23	(0.84-1.80)
>44	4	10	0.73	(0.23-2.34)	7	7	1.93	(0.64-5.81)
Birth order								
1st	559	1081	1.00		436	771	1.00	
2nd	400	795	0.94	(0.79-1.11)	227	501	0.76*	(0.62-0.94)
3rd	171	341	0.96	(0.76-1.22)	127	295	0.73*	(0.55-0.95)
4th	76	169	0.81	(0.59-1.12)	66	166	0.66*	(0.47-0.94)
5th	34	66	0.93	(0.58-1.48)	48	82	0.99	(0.65-1.50)
6th+	32	85	0.70	(0.44-1.11)	39	84	0.68	(0.43-1.06)

*p<0.05

a)



b)

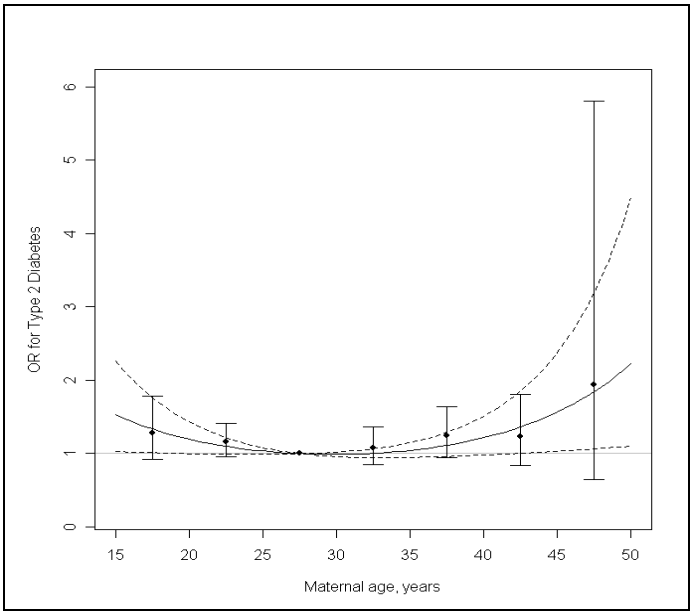


Figure 8. ORs for a) T1DM and b) T2DM according to maternal age.
Estimated continuous model (black line) with 95% CI (dashed lines) and categorical models (circles). The quadratic term in b) was found to be significant.

5.3 The effects of perinatal exposures on the risk for young adult-onset diabetes

Paper IV

Recorded data on possible perinatal risk factors were available for 858 case-control pairs of T1DM and 355 case-control pairs of T2DM, and all these pairs were included in the analysis. Pregnancies with multiple fetuses were excluded. As data on newborns including weight and length were available in both birth records and child welfare clinic records, both of them were used. Birth records were used as the primary data source for birth weight and birth length. For individuals with an unavailable birth record, the child welfare clinic record was used as the data source. The demographic and anthropometric characteristics of the study subjects are presented in Table 7.

Table 7. Mean values (SD) of the characteristics of the study subjects.
Grey areas indicate significant differences (according to t-test) in mean values between cases and controls.

		Men		Women	
		Cases	Controls	Cases	Controls
T1DM	Age at diagnosis	26.4 (6.98)		26.0 (7.31)	
	Birth weight, kg	3.6 (0.56)	3.6 (0.50)	3.5 (0.48)	3.5 (0.5)
	Birth length, cm	50.8 (2.32)	50.8 (2.11)	49.9 (1.97)	50.1 (1.99)
	Gestational age, d	278.7 (13.44)	279.3 (13.76)	278.8 (12.76)	278.8 (13.00)
	Placental weight, kg	0.6 (0.13)	0.6 (0.13)	0.6 (0.12)	0.6 (0.12)
	Maternal height, cm	163.1 (5.27)	162.3 (5.62)	162.3 (5.25)	162.7 (5.63)
	Maternal weight, kg	59.2 (8.71)	58.0 (8.94)	58.9 (8.41)	59.1 (9.04)
T2DM	Age at diagnosis	35.0 (3.96)		33.2 (4.73)	
	Birth weight, kg	3.4 (0.60)	3.6 (0.55)	3.3 (0.62)	3.4 (0.49)
	Birth length, cm	50.2 (2.49)	50.7 (2.41)	49.6 (2.19)	50.1 (1.99)
	Gestational age, d	277.1 (15.71)	276.8 (15.01)	280.2 (15.12)	275.4 (20.39)
	Placental weight, kg	0.6 (0.12)	0.6 (0.13)	0.6 (0.12)	0.6 (0.13)
	Maternal height, cm	160.7 (5.42)	161.1 (5.88)	160.7 (6.61)	161.4 (5.34)
	Maternal weight, kg	59.6 (9.53)	60.3 (6.84)	58.9 (10.70)	59.2 (8.45)

Results of the conditional logistic regression showed that none of the examined perinatal factors (body size at birth, placental weight, gestational age, and maternal body size) influenced the risk for young adult-onset T1DM. Adjusting placental weight for birth weight did not affect the results. Results of the continuous linear model for T1DM are reported in Table 8.

Table 8. Odds ratios (ORs) for T1DM in young Finnish adults by the examined perinatal exposures (linear model)

Examined variable	Adjusted for	OR (95% CI)	p-value	n
Birth weight (per 1 kg)		0.92 (0.77-1.10)	0.31	2663
Birth length (per 1 cm)		0.99 (0.95-1.03)	0.57	2533
BMI at birth (per 1 kg/m^2)		0.96 (0.89-1.03)	0.21	2529
PI at birth (per 1 kg/m^3)		0.98 (0.94-1.02)	0.28	2529
Placental weight (per 100 g)		0.94 (0.84-1.05)	0.29	1410
Placental weight (per 100 g)	Birth weight	1.00 (0.86-1.15)	0.95	1405
Gestational age (per d)		1.00 (0.99-1.00)	0.38	1667
Maternal weight prior to pregnancy (per 1 kg)	Birth weight	1.02 (0.996-1.03)	0.12	954
Maternal height (per 1 cm)	Birth weight	1.02 (0.997-1.05)	0.08	1401
Maternal BMI (per 1 kg/m^2)	Birth weight	1.03 (0.97-1.10)	0.28	860
Maternal weight prior to childbirth (per 1 kg)	Birth weight	1.01 (0.99-1.02)	0.46	1440

The association between birth weight and the risk for T2DM was estimated using three alternative models. According to the conditional logistic regression model with a linear regression term, the OR for T2DM was 0.61 (95% CI 0.47-0.79) per 1 kg increase in birth weight ($p<0.001$) (Table 9). The quadratic model for birth weight was not significant. The piecewise linear model (Figure 9) showed that the risk for T2DM decreased until the birth weight of 4.2 kg (95% CI 3.05-5.55 kg) and then began to increase. The OR for T2DM was 0.49 (95% CI 0.37-0.66) per 1 kg increase in birth weight until 4.2 kg ($p<0.001$), and from 4.2 kg onwards the OR for T2DM was 4.8 (95% CI 1.32-17.62) per 1 kg increase in birth weight ($p=0.018$). With birth weights higher than 4.2 kg, the interaction between sex and birth weight was statistically significant. When men and women were examined separately, the increased risk for T2DM after 4.2 kg was not significant in men. In women the increase in the risk for T2DM remained significant, but because the number of cases was small the OR was unreliable. The piecewise linear model displayed the best fit as measured by AIC. The AIC's for the linear, quadratic and piecewise linear models were 638.8, 635.0 and 630.9 respectively. Gestational age did not have an

effect on the subsequent risk for T2DM and therefore birth weight was not adjusted for gestational age.

Table 9. Odds ratios (ORs) for T2DM in young Finnish adults by the examined perinatal exposures.

Model	Examined variable	Adjusted for	OR (95% CI)	p-value	n
Piecewise linear	Birth weight <4.2 kg (per 1 kg)		0.49 (0.37-0.66)*	<0.01	1045
	Birth weight ≥4.2 kg (per 1 kg)		4.8 (1.32-17.62)*	0.018	91
	♂ Birth weight <4.2 kg (per 1 kg)		0.50 (0.34-0.72)*	<0.01	593
	♂ Birth weight ≥4.2 kg (per 1 kg)		1.74 (0.38-8.07)	0.48	69
	♀ Birth weight <4.2 kg (per 1 kg)		0.42 (0.26-0.69)*	<0.01	452
	♀ Birth weight ≥4.2 kg (per 1 kg)		>20 (95% CI lower limit)*	<0.01	22
Linear	Birth weight (per 1 kg)		0.61 (0.47-0.79)*	<0.01	1136
	Birth length (per 1 cm)		0.88 (0.81-0.95)*	<0.01	963
	BMI at birth (per 1 kg/m^2)		0.81 (0.73-0.90)*	<0.01	962
	PI at birth (per 1 kg/m^3)		0.91 (0.86-0.97)*	<0.01	962
	Placental weight (per 100 g)		0.77 (0.61-0.98)*	0.03	341
	Placental weight (per 100 g)	Birth weight	0.80 (0.61-1.06)	0.12	340
	Gestational age (per d)		1.00 (0.99-1.02)	0.72	529
	Maternal weight prior to pregnancy (per 1 kg)	Birth weight	1.02 (0.95-1.10)	0.53	129
	Maternal height (per 1 cm)	Birth weight	0.98 (0.94-1.03)	0.45	348
	Maternal BMI (per 1 kg/m^2)	Birth weight	1.32 (1.00-1.74)*	0.047	110
	Maternal weight prior to childbirth (per 1 kg)	Birth weight	1.03 (0.99-1.07)	0.17	366

*p<0.05 ♂men ♀women

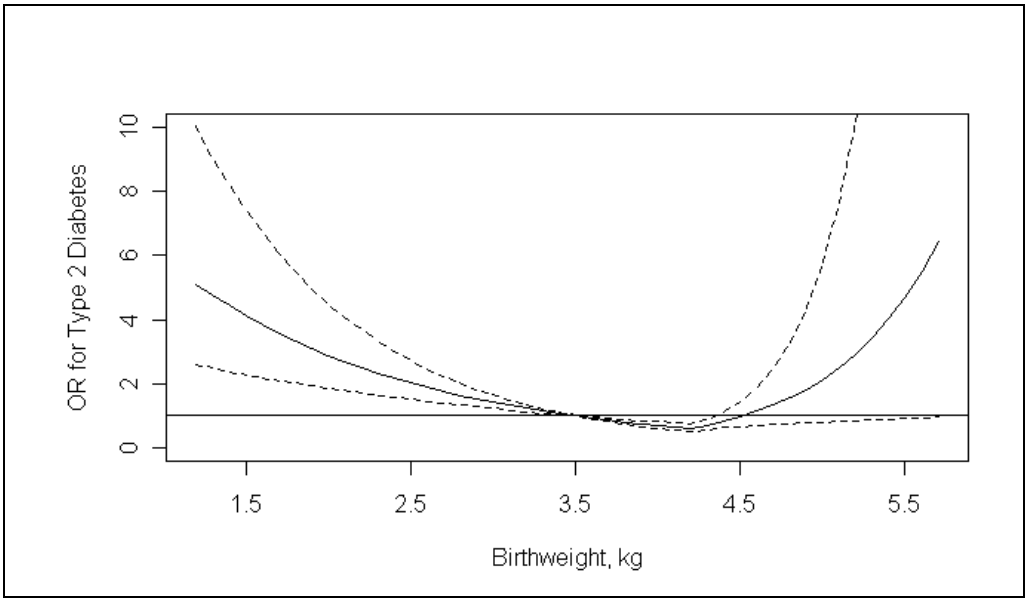


Figure 9. Odds ratio (OR) for young adult-onset T2DM by birth weight (black line) with 95% CIs (red lines). The piecewise linear model.

In addition to the analysis of the effect of birth weight on the risk for T2DM, the effects of birth length, BMI, and ponderal index (PI) at birth were also examined. The ORs for T2DM were 0.88 (95% CI 0.81-0.95) for every 1 cm increase in birth length ($p<0.001$), 0.81 (95% CI 0.73-0.90) per 1 kg/m^2 increase in BMI at birth ($p<0.001$), and 0.91 (95% CI 0.86-0.97) per 1 kg/m^3 increase in PI at birth ($p=0.0031$).

The risk for T2DM was lower in children with large placentae, the OR for T2DM was 0.77 (95% CI 0.61-0.98) per 100 g increase in placental weight ($p=0.03$). However, when adjusted for birth weight, the effect of placental weight was no longer significant. The effects of maternal body size (height, weight, BMI prior to pregnancy, and weight prior to childbirth) were examined, and no associations with the risk for T2DM in the offspring were found. When adjusted for birth weight, the OR for T2DM was 1.32 (95% CI 1.00-1.74) per 1 kg/m^2 increase in maternal BMI before pregnancy ($p=0.047$).

5.4 The effect of childhood BMI trajectories on the risk for young adult-onset diabetes

Paper V

From the 4,440 child welfare clinic records obtained, it was possible to form 607 case-control pairs with T1DM and 324 case-control pairs with T2DM for whom child welfare clinic records were available for the diabetes patient and for at least one of the controls. Twenty individuals were excluded as they had no valid anthropometric observations. Only the case-control pairs with sufficient growth data to estimate the BMI growth curve (at least three height and weight measurements within a time axis that permitted the fitting of the quadratic function) were included in the analyses, and therefore the final number of case-control pairs was 218 (160 with one control and 58 with two controls) for T1DM and 64 (52 with one control and 12 with two controls) for T2DM. The average number of measurements (height and weight) per child was 7.3 (0-32) between ages 0-3 years, 5.7 (0-22) between 3-11 years, and 3.8 (0-19) for those over 11 years of age. Visually, the BMI growth trajectories of the patients with young adult-onset T1DM were close to those of their controls (Figure 10).

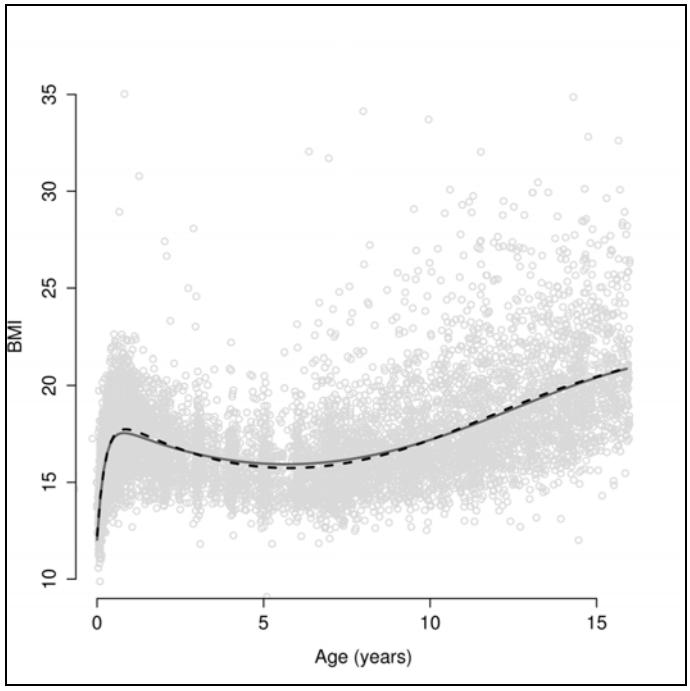


Figure 10. BMI growth curves of cases of T1DM and their controls.
Cases (dashed line), controls (solid line), individual observations (grey circles). BMI values are kg/m^2.

The analysis of BMI characteristics among case-control pairs with T1DM showed that the risk for T1DM increased 1.19-fold with every 1 kg/m^2 increase in the infancy maximum BMI between ages 0-2 years (p=0.02). There were no age differences in the timing of the infancy maximum BMI. In addition, the level of BMI at the BMI rebound between ages 3-11 was similar in individuals with T1DM and control subjects. The age of the BMI rebound between ages 3-11 was slightly but not significantly lower in individuals with T1DM. Adjusting the BMI analysis for birth weight did not significantly affect the results. The odds ratios describing the effect sizes for the examined childhood BMI characteristics on the risk for young adult-onset T1DM are presented in Table 10. (The maximum BMI in infancy and the BMI rebound are illustrated in Figure 2.)

Table 10. The odds ratios (ORs) for young adult-onset T1DM according to childhood BMI characteristics (218 cases and 276 controls)

Examined characteristic	OR (95% CI)	p-value	OR (95% CI)*	p-value*
Maximum BMI during the first 2 years of age (per 1 kg/m^2)	1.19 (1.03-1.36)	0.02	1.21 (1.05-1.41)	0.01
Age at maximum BMI (per year)	1.16 (0.82-1.65)	0.41	1.14 (0.80-1.64)	0.48
Minimum BMI at 3 to 11 years of age (per 1 kg/m^2)	0.90 (0.73-1.10)	0.29	0.88 (0.70-1.09)	0.23
Age at minimum BMI (per year)	0.87 (0.75-1.02)	0.09	0.88 (0.75-1.03)	0.11

*Adjusted for birth weight

The data analysis of the case-control pairs with T2DM showed that the infancy maximum BMI and the age at the infancy maximum BMI between ages 0-2 years were similar between the cases and the controls. The risk for T2DM was strongly affected by the level of BMI at the BMI rebound. A gain of 1 kg/m^2 in the minimum BMI increased the risk for T2DM 1.77-fold (p=0.04). The effect became stronger when adjusted for birth weight: the risk for T2DM increased 1.87-fold per every 1 kg/m^2 gain in the minimum BMI (p=0.04). In individuals with T2DM, the BMI rebound seemed to occur at a younger age, but the effect was not statistically significant. An excess BMI gain in individuals who develop young adult-onset T2DM already began in early childhood after the age of the BMI rebound. The risk for T2DM increased 12-fold (95% CI 1.68-88.3, p=0.013) for every 1 (kg/m^2)/year increase in the rate of BMI gain between the age of the BMI rebound and 11 years. The odds ratios for young adult-onset T2DM according to childhood BMI characteristics are presented in Table 11. Visually, the growth patterns of the patients with young adult-onset T2DM were prominently aberrant (Figure 11).

Table 11. The odds ratios (ORs) for young adult-onset T2DM according to childhood BMI characteristics (64 cases and 76 controls)

Examined characteristic	OR (95% CI)	p-value	OR (95% CI)*	p-value*
Maximum BMI during the first 2 years of age (per 1 kg/m^2)	0.91 (0.59-1.41)	0.69	0.93 (0.59-1.48)	0.77
Age at maximum BMI (per year)	0.69 (0.28-1.70)	0.42	0.79 (0.29-2.07)	0.63
Minimum BMI at 3 to 11 years of age (per 1 kg/m^2)	1.77 (1.04-3.00)	0.04	1.87 (1.04-3.37)	0.04
Age at minimum BMI (per year)	0.75 (0.53-1.06)	0.11	0.75 (0.52-1.09)	0.13

*Adjusted for birth weight

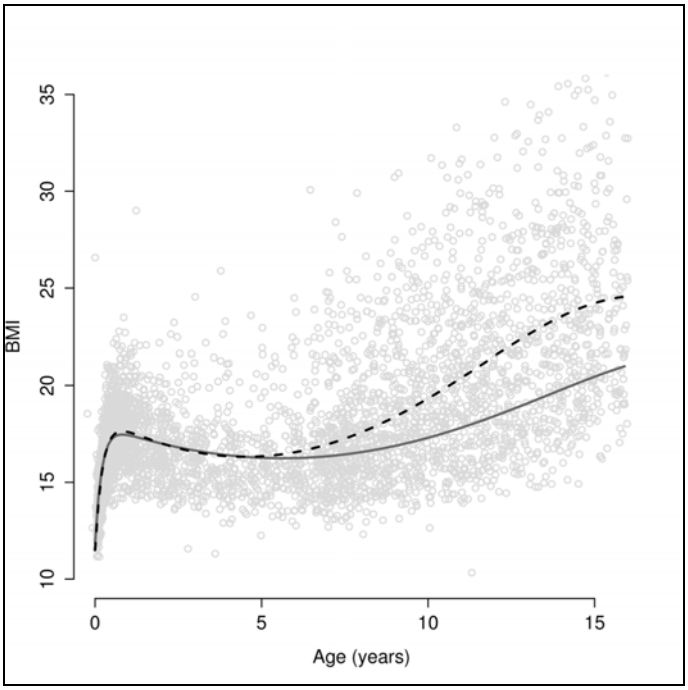


Figure 11. BMI growth curves of cases of T2DM and their controls.
Cases (dashed line), controls (solid line), individual observations (grey circles). BMI values are kg/m^2.

Information about the duration of breastfeeding was available in 21.5% of the records (of the original 607 case-control pairs of T1DM and 324 case-control pairs of T2DM). It was on average 2.9 months (0-43 months). Both the duration of breastfeeding and the status of breastfeeding versus bottle feeding were compared, and there were no differences between the cases of T1DM and T2DM and their respective controls in the status or duration of breastfeeding (Table 12).

Table 12. The odds ratios (ORs) for young adult-onset T1DM and T2DM according to feeding practice in infancy

	Examined variable	OR (95% CI)	p-value	Number of observations
T1DM	Months of breastfeeding (per 1 mo)	0.97 (0.92-1.02)	0.25	916
	Status of breastfeeding (yes vs. no)	0.96 (0.53-1.73)	0.88	916
T2DM	Months of breastfeeding (per 1 mo)	0.93 (0.83-1.05)	0.26	374
	Status of breastfeeding (yes vs. no)	0.81 (0.33-2.00)	0.64	374

6 Discussion

6.1 Diabetes incidence and trends among young Finnish adults

Type 1 diabetes

The results of this population-based study showed that the high risk for T1DM among Finnish individuals extends to at least 39 years of age. The average incidence of T1DM among 15-39-year-old Finns during 1992-2001, 18.0 per 100,000/year, was higher than previously reported of other European populations (96, 101, 102, 104) (Table 2). The average incidence in Sardinia has been reported to be slightly higher, 18.8 per 100,000/year (94), but the Sardinian data only included individuals up to the age of 29. Comparing incidence rates internationally is difficult, as the incidence rates from most other countries are from an earlier period. However, a small study in Kronoberg county (Sweden) (108) comprised a comparable period from 1998 to 2001, and the incidence of T1DM among young adults observed there was close to the incidence observed in this study among young Finnish adults (Table 2).

Although the incidence of T1DM among young Finnish adults during 1992-2001 was high on a global scale, it was considerably lower than among Finnish children during the same period (91). The age distribution of new cases of T1DM in Finland (Figure 12) was similar to the age distribution in other European populations with a high incidence of T1DM (102). It has been shown that in the areas with a high incidence of childhood-onset T1DM, the incidence falls steeply after 15 years of age, whereas in the populations with a lower incidence of childhood-onset T1DM, the incidence decreases gradually with age or remains on the same level as observed in childhood (102). This phenomenon may indicate a more aggressive disease progression among individuals living in high incidence areas, causing a larger proportion of all T1DM cases to appear already before the age of 15.

The observed 1.7-fold male predominance in the incidence of T1DM among young Finnish adults is consistent with the results from other countries (93, 96, 105, 109). The cause for the male predominance is unknown. Differences in susceptibility to viral infections (96), and a metabolic burden caused by android fat distribution (102) have been suggested as possible explanations.

Globally, the incidence of T1DM among children under the age of 15 has been increasing for decades (83), and thus it can be assumed that the same phenomenon

also prevails among older individuals. According to this study, the incidence of T1DM among young Finnish adults increased on average 3.9% per year during 1992-2001, which is comparable to the 4.2% average annual increase observed in Finnish children during the same period (6). Thus, there is no evidence that the incidence of T1DM in Finnish children would be increasing merely due to the younger age of diabetes onset, as suggested with regard to Swedish children (263). However, a longer observation period is needed in order to draw definitive conclusions on whether the incidence of T1DM is permanently increasing among young Finnish adults, as the incidence trends may show fluctuation over time. For example, a comparison to an earlier Finnish study (82) suggests that the incidence of T1DM among 15-19-year-old Finns has not changed in the course of 20 years (24.1 per 100,000/year between 1970-1979 vs. 23.9 per 100,000/year between 1992-2001).

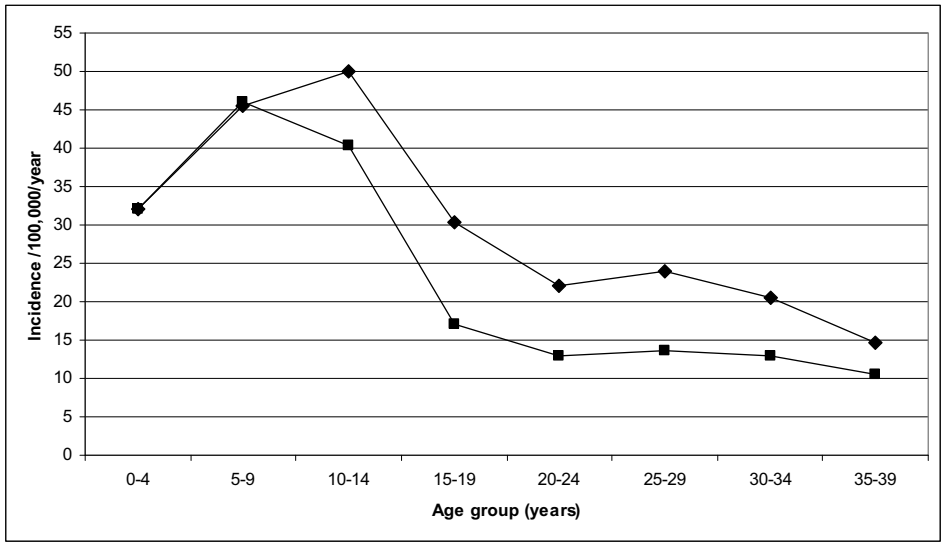


Figure 12. The incidence of T1DM in Finnish children and young adults. Incidence for age groups 0-4, 5-9, and 10-14 years are adopted from Rytkönen (91). Males (diamonds) and females (squares).
Note: Data for 0-14-year-old individuals is for the years 1987-2001 and collected with a different method (91).

Type 2 diabetes

The results concerning the incidence of T2DM confirmed that the epidemic of youth-onset T2DM has reached Finland. The total age-adjusted incidence of young adult-onset T2DM was 12.9 per 100,000/year, indicating that a considerable number of Finns are diagnosed with T2DM before the age of 40. Although the incidence of T2DM was still low in the youngest examined age groups, it started to increase rapidly after the age of 30, especially in men. Due to the register-based approach of this study, all the cases with T2DM treated only with lifestyle counseling could not be captured, and this study provided no information on the undiagnosed cases of T2DM. Therefore, the incidence estimates for T2DM reported within this study are conservative.

Although the highest numbers of youth-onset T2DM have been reported in non-Europid ethnic groups, the age of diagnosis of T2DM has also decreased in populations of Europid origin (123). The incidence rates of T2DM are difficult to compare between countries, as most previous studies on the occurrence of T2DM are based on prevalence rates or are case studies. However, the incidence of young adult-onset T2DM in Finland is low compared to the recent incidence data from the USA (128). The incidence of T2DM was 5.6 per 100,000/year among the 15-19-year-old population of Europid origin in the USA, whereas according to this study, the incidence of T2DM among the same age group in Finland was only 0.7 per 100,000/year.

The incidence of T2DM among young adults increased rapidly during the ten-year study period: the average annual increase in incidence was 4.3%. Since the standardized forms, filled in at hospitals and primary care clinics, were not available for the second half of the study (1997-2001), this may have caused cases of T2DM to fall out from the end of the study period. Therefore, the estimated annual increase of 4.3% per year was, albeit high, probably underestimated. This increase in young adult-onset T2DM among Finns is in accordance with reports of an emerging worldwide epidemic of youth-onset T2DM (2, 122, 132), and further supported by observed increases in obesity (135) and metabolic syndrome (138) among the Finnish youth. As T2DM takes years to develop, health problems in these individuals may begin as early as in their teens. When an increasing number of young adults are already diagnosed with T2DM at the beginning of working age, this disease inflicts an unfavorable effect on the health of the working population. On average 200 Finns of less than 40 years of age are diagnosed with T2DM annually, and this number increases by ten individuals each year. If this increasing trend cannot be reversed, young adult-onset T2DM among Finns will become a major public health problem in the near future.

Undefined diabetes
The type of diabetes remained undefined in approximately 16% of the cases included in this study. This amount is comparable to the estimated amount of LADA (25% of individuals with a diagnosis of T2DM before the age of 34) (264). However, all of the 1,021 individuals classified as having undefined diabetes in this study are probably not cases of LADA; among them are also cases of T2DM with inadequate information for classification. This assumption is supported by the higher incidence of undefined diabetes in older age groups. As blood was not drawn from the study subjects, a more precise classification based on autoantibody and C-peptide measurements was not possible in this study.

The incidence of undefined diabetes remained stable during 1992-2001, indicating that the observed increases in the incidence of T1DM and T2DM during the same period were not caused by classification bias.

6.2 Perinatal and early childhood exposures

The analysis of the effects of perinatal exposures was divided in two parts: maternal age and birth order (paper III) and other perinatal exposures (paper IV). The objective of this was to include as many case-control pairs as possible in each analysis. As data on maternal age and birth order could be obtained from the National Population Register, almost all of the diabetes cases diagnosed during 1992-1996 and their controls could be included in the analyses presented in paper III. The availability of data on other perinatal exposures analyzed in paper IV was, however, dependent on the availability of birth records and child welfare clinic records, and therefore these analyses formed another logical entity. In paper V, the focus was on postnatal growth.

6.2.1 Perinatal and early childhood exposures and the risk for young adult-onset T1DM

According to the results of this study, perinatal exposures such as maternal age, parity, or body size at birth did not have any effect on the incidence of young adult-onset T1DM. This observation is in agreement with earlier studies that have emphasized the age of diabetes onset: the risk-modifying effects of maternal age (166), birth order (169), and birth weight (204) have all been reported to be restricted to very young-onset cases of T1DM. Gestational age, placental size or maternal body size did not have any effect on the incidence of young adult-onset T1DM in this study either. It appears that in young adult-onset T1DM, the

environmental factors triggering β-cell destruction do not operate in the perinatal period, but rather later in life.

Instead, previous findings indicating that a high BMI in infancy increases the risk for childhood-onset T1DM (12, 209) are confirmed, and the results of this study show that this also applies to young adult-onset cases. Fast BMI growth in infancy among these individuals may be caused by a common genetic trait between growth and T1DM, or by nutritional factors. However, as a nutritional factor in infancy, the duration of breastfeeding did not explain the risk in our dataset. As there is a long time period between breastfeeding and young adult-onset T1DM, the possible effect of breastfeeding on the development of T1DM may be weaker than in childhood-onset cases, and therefore undetectable. Unlike in childhood-onset T1DM (12), differences in BMI between cases of young adult-onset T1DM and their control individuals leveled out by the age of the BMI rebound. Therefore, it is unlikely that the increasing incidence of young adult-onset T1DM in Finland would be caused by increasing overweight in Finnish adolescents.

6.2.2 Perinatal and early childhood exposures and the risk for young adult-onset T2DM

The analysis including 1,072 case-control pairs of T2DM revealed a U-shaped association between maternal age and the risk for T2DM in the offspring. In addition, second to fourth born children were observed to have a lower risk for T2DM compared to the firstborn. The observed differences in the risk for T2DM attributed to maternal age or birth order were small.

The most feasible explanation for these observations is the effect of maternal age and parity on birth weight: firstborn children are generally smaller than the subsequent ones (185). In addition, intrauterine growth retardation and prematurity, both resulting in low birth weight, are more frequent at the extremes of maternal age (265). The possible confounding effect of birth weight would have been interesting to explore further, but this was not possible within this study due to the lack of data on birth weight for part of the study subjects.

The results of this study confirmed earlier observations of an increased risk for T2DM in individuals born with low birth weight (221, 227). In addition to low birth weight, shortness, a low BMI, and a low PI at birth were found to be risk factors for young adult-onset T2DM. The association between low birth size and T2DM may be caused by in utero programming of a thrifty metabolism (220). However, other possible explanations, such as epigenetic modification (250) and gene-environment interactions (251), also need to be considered.

Because it has been argued that the relationship between birth weight and T2DM may not be linear (231, 232), other models were also fitted to the birth weight data in this study. The best fit was achieved with the piecewise linear model, which indicated that the risk for T2DM may also be elevated in very high birth weight babies. However, a larger number of study subjects are needed in order to define the "threshold" birth weight after which the risk for type 2 diabetes starts to increase. The increased risk for T2DM among individuals born with high birth weight may be caused either by the metabolic effects of maternal hyperglycemia, a genetic susceptibility to T2DM inherited from the mother, or both.

Birth weight is affected by the fetal nutritional supply via the placenta. Indirect information on the placental transfer capacity can be obtained by measuring the placental size (266). In this study, low placental weight increased the risk for T2DM, but this effect was no longer significant after adjusting for birth weight. Therefore, it seems that the variation in birth weight explains the increased risk in persons born with small placentae. On the other hand, it is also possible that there are some other factors, such as genetic growth potential or maternal nutrition during pregnancy, affecting both birth weight and placental weight. According to this study, a high pregestational BMI in the mother increased the offspring's risk for T2DM independently of birth weight. The reason for this may be a genetic predisposition to obesity and T2DM in both the mother and the child.

In accordance with earlier observations (11, 236), the average age of the BMI rebound was slightly (non-significantly) lower in individuals with T2DM than in their control subjects. It has been suggested that the early BMI rebound may result from lower lean mass in the individuals with T2DM (11). The results of this study also demonstrated an increased risk for T2DM to be related to the level of BMI at the time of the BMI rebound, indicating that the total weight gain from birth to the BMI rebound was greater in individuals with T2DM. In agreement, a British-Chilean study showed that compared to infants born appropriate for gestational age, infants born small for gestational age did not have insulin resistance at birth, but developed it during their first 3 years of life. This transition was associated with rapid postnatal weight gain (267).

In this study, the rapid increase in BMI in individuals with T2DM already began at a very young age after the age of the BMI rebound. The rapid increase of BMI in adolescence associates strongly with central obesity in adults (268), which in turn markedly increases the risk for T2DM. In this study, low birth weight predicted a high BMI at the time of the BMI rebound, which preceded rapid BMI growth thereafter. Therefore, it appears that low birth weight may cause T2DM in young Finnish adults at least in part through programming an increased tendency for adult

central obesity. A high BMI at the BMI rebound may only be an intermediate phase in this progression.

Previous findings concerning the protective effect of breastfeeding against T2DM (240, 269) could not be confirmed in this study. The possible effect of breastfeeding may be too weak to be detected by retrospective data collection, as information on breastfeeding was only recorded in a minority of the child welfare clinic records. Although the used case-control setting is efficient in reducing variations in the quality of data (such as different practices between child welfare centers), it is possible that the duration of breastfeeding was recorded more often if a child was growing aberrantly, causing bias in the data selection.

The perinatal risk factors for young adult-onset T2DM observed in this study - maternal age extremes, low and very high birth weight, and rapid BMI gain in childhood - have potential effects on public health. The long-term health effects of low birth weight are affecting elderly people today. However, instead of low birth weight, the adverse effects of high birth weight, high maternal age, and rapid BMI gain in childhood may be emphasized among Finns in the future. An increasing prevalence of GDM (270), a rising proportion of parturients aged >35 years (271), and increasing childhood obesity (135, 136) may elevate the risk for T2DM among new generations of young Finnish adults. However, whilst preventing low birth weight is difficult, interventions against GDM and childhood obesity are feasible and should be acted upon.

6.3 Methodological considerations

The methodological aspects of the chosen study design, an incidence study conducted in a Finnish cohort followed by an incident case-control study, need to be discussed. When conducting an incidence study in Finland, where precise demographic data is readily available, the main methodological concern is the completeness of case-ascertainment. In addition, when evaluating the validity of the following case-control study, the quality of the exposure data, the methods of case-control selection, and statistical power need to be assessed. Finally, although the exposure data (such as birth weight) in this study were recorded prospectively, the tracing of the records was retrospective, which needs to be taken into consideration.

The accuracy and coverage of the Finnish national healthcare registers have been confirmed to be excellent (5, 272). For example, the overall sensitivity of the Hospital Discharge Register (HDR) in detecting diagnoses of myocardial infarction has been reported to be 83%, and the positive predictive value was 90% (5). In addition, the Drug Reimbursement Register (DRR) is a reliable data source, because the reimbursement of medication costs provides the patient with a marked financial benefit and consequently most patients with drug-treated diabetes apply for this.

Despite the good quality of the Finnish register data, there are several aspects that need to be considered regarding the trends in incidence observed in this study. While it can be assumed that >90% of cases with young adult-onset T1DM could be captured with the applied method (insulin purchases are found in the Drug Prescription Register (DPR) and entitlement to free-of-charge medication is found in the DRR), some of the new cases of young adult-onset T2DM were probably missed. As discussed above, undiagnosed cases of T2DM could not be captured with this register-based method. Therefore, the results of this study should be interpreted as concerning only diagnosed cases of T2DM, whilst the proportion of undiagnosed cases is estimated to be substantial (44). Data obtained from the DPR did not cover the first two years of the study period, which may have caused some cases of T2DM, which were not reported by diabetes nurses or listed in the HDR, to fall out from the first study years thereby heightening the upward trend in the incidence of T2DM. On the other hand, the standardized forms filled in by diabetes nurses were not collected in the second half of the study, leading to the opposite effect on the observed trend. In addition, the threshold FPG for the diagnosis of diabetes was lowered in 1997, which probably increased diagnoses thereafter. Due to the above mentioned reasons, although all the evidence obtained from this study and other Finnish studies (which examine other health indicators such as obesity among the Finnish youth) refers to an increasing trend in young adult-onset T2DM, the exact rate of the increase needs to be confirmed with a longer study period. The

prevention programme for T2DM in Finland, the D2D project of the Development Programme for the Prevention and Care of Diabetes in Finland (DEHKO) (7), was not launched until 2003, and therefore did not influence the incidence of T2DM during this study period.

Regarding the analysis of the effects of maternal age and birth order, Finland is the optimal place to conduct this kind of study: the unique personal identification number, assigned to every Finnish resident in the early 1970s and since then assigned at birth or after immigration, allows the unequivocal identification of the study subjects and their relatives from the National Population Register. However, it was only possible to detect nuclear families, and half-siblings were not included in the analyses. As a result, the sizes of the examined families were smaller than in reality, and the number of first-borns was exaggerated. It is unlikely that this had any effect on the results, as the same was true for the control families.

The anthropometric data used for examining the effects of perinatal exposures and childhood growth was not subjected to recall bias because it was obtained from official records filled in by healthcare professionals and validated by comparing records of the same person. However, this data was missing for part of the study subjects. Due to the fact that the child welfare and birth records were filed in a large number of different archives, only 40% of the birth records and 47% of the child welfare clinic records searched for were found. The shortage of data for the case-control pairs with T2DM was more substantial. The reason for this was the older average age of individuals with T2DM (and their birth date matched control individuals), which is why their child welfare clinic records and birth records were more difficult to trace. Fortunately, there is no reason to expect that the examined perinatal factors would vary depending on whether the record was later found or not. Because the child welfare clinic records were only collected from the 200 largest municipalities, the case-control pairs were matched by place of birth in order to avoid possible bias caused by the lack of data from sparsely populated areas.

Only the case-control pairs with sufficient records of growth data could be included in the BMI growth analysis. Due to the retrospective approach of this study, it is possible that individuals with aberrant growth patterns were measured more frequently than individuals who were growing on the standard curve, and therefore they were included in the study more often. The case-control setting of this study is efficient in reducing the possible errors caused by the uneven frequency of measurements, as it was confirmed that the reason for the exclusion of a case-control pair was equally often the shortage of data for the case as for the control. This indicates that there was a corresponding proportion of extra-frequently measured (i.e. possibly aberrantly growing) case and control individuals in the examined dataset.

Like in all studies, it is important to consider whether the statistical power of this study was adequate enough to detect the explored phenomenon. In this study, birth weight was not found to have any effect on the risk for young adult-onset T1DM. In order to examine the statistical power of this analysis, the statistical power of the study was evaluated as a function of the effect size (Figure 13). The results of this simulation showed, for example, that a 40% increase (or decrease) in the risk for T1DM per 1 kg change in birth weight would have been detectable by a probability of 80% with the chosen significance level of 5%. It can therefore be concluded that the study's statistical power was adequate enough to show clinically relevant effects on the risk for T1DM attributed to birth weight.

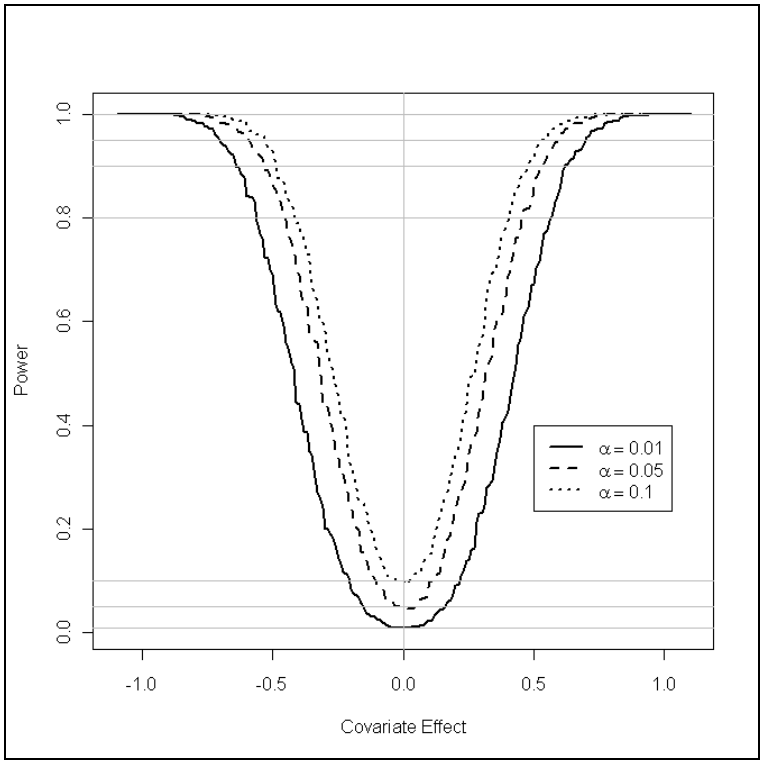


Figure 13. Statistical power of the study as a function of the effect size for three different significance levels, α.
The curves are numerically evaluated for the linear model of the effect of 1 kg additional birth weight on the log-odds-ratio for T1DM. The simulations are done for 1,000 case-control pairs (assuming that the birth weights in the populations are normally distributed with mean and SD estimated from the total sample).

Within this study, it was not possible to control for all the confounding factors that may influence the association between the examined perinatal exposure and young adult-onset diabetes. Information on socio-economic factors during childhood was available for the study, as the father's occupation was recorded in the majority of the healthcare records. However, the study subjects were born within a long time period (1952-1981), during which the socio-economic structure of the Finnish population changed essentially, making adjustment for social class impossible. During the study period, virtually all of the pregnant mothers attended regular examinations in ante-natal clinics and took their newborns to child welfare clinics, thus decreasing the differences in health care use between social classes.

The potential effects of parental diabetes could not be examined in this study. In the birth records, only 39 out of 3,812 mothers were recorded as having diabetes or glucosuria during pregnancy, which was not considered sufficiently reliable information to be included in the analyses. As there is a significant predisposition to both types of diabetes, it can be assumed that there were more diabetic parents in the families of the diabetes cases than in the control families, and maternal diabetes may have caused the increased risk for T2DM observed in individuals born with very high birth weight.

7 Conclusions

This is the first study to provide population-based information on the incidence of both T1DM and T2DM among young Finnish adults. In addition, the possible risk factors for young adult-onset T1DM and T2DM related to the conditions during early life are extensively explored within this study.

The conclusions related to the specific aims are:

- The risk for T1DM among the Finnish population remains high throughout young adult age. During the years 1992-2001, the incidence of T1DM among young Finnish adults increased annually by 3.9%.

- Approximately 200-300 young Finnish adults under the age of 40 are annually diagnosed with T2DM. Moreover, concomitantly with increasing obesity and decreasing physical activity among the Finnish youth, the incidence of young adult-onset T2DM increased by 4.3% per year in Finland during 1992-2001.

- Rapid growth during the first years of life may be a risk factor for young adult-onset T1DM.

- Conditions during fetal development and childhood are associated with the risk for young adult-onset T2DM. Better knowledge of the developmental programming of T2DM will aid better risk profiling and individualized lifestyle counseling.

- The primary prevention of T2DM should also focus on the prevention of childhood and adolescent obesity, as the excess weight gain in individuals with T2DM already begins during early childhood.

8 Future directions

- In order to assess the public health implications of young adult-onset diabetes, monitoring the incidence of T1DM and T2DM among young Finnish adults should be continued, and the prevalence of T2DM among young Finnish adults should be investigated.

- Results obtained from studies examining childhood-onset T1DM cannot necessarily be applied to cases of T1DM diagnosed after the age of 15. Possible environmental risk factors for T1DM should also be studied in patients diagnosed in young adulthood, as these may be different than in childhood-onset cases.

- Possibilities of applying the increasing knowledge of the associations of fetal and childhood development on the risk for T2DM to primary prevention should be examined.

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Niina Lammi

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Appendix 1. ICD-9 and ICD-10 codes relevant for the study

	ICD-9		ICD-10	
T1DM	2500B	Insulin-dependent diabetes no complications	E10.9	Type 1 diabetes no complications
	2501B-2508B	Insulin-dependent diabetes with complications	E10.0-E10.8	Type 1 diabetes with complications
			O24.0	Insulin-treated diabetes diagnosed before pregnancy
T2DM	2500A	Non insulin-dependent diabetes no complications	E11.9	Type 2 diabetes no complications
	2501A-2508A	Non insulin-dependent diabetes with complications	E11.0-E11.8	Type 2 diabetes with complications
			O24.1	Non insulin-treated diabetes diagnosed before pregnancy
DM	2500C	Maturity-onset diabetes of the youth	E13	Other diabetes
	2500X	Non specified diabetes	E14	Non specified diabetes
			E12	Diabetes related to malnutrition
			G59.0	Diabetic mononeuropathy
			G62.2	Diabetic polyneuropathy
			G99.0	Autonomic neuropathy
			G73.0	Diabetic amyotrophy
			H28.0	Diabetic cataract
			H36.0	Diabetic retinopathy
			I79.2	Peripheric angiopathy
			M14.6	Neuropathic arthropathy
			N08.3	Diabetic nephropathy

DM			O24.2	Malnutrition-related diabetes before pregnancy
			O24.3	Non specific diabetes before pregnancy
			P70	Transient disorders of carbohydrate metabolism in newborn
			R73	Hyperglycemia
GDM	6480A	Gestational diabetes	O24.4	Gestational diabetes
	6488A	Abnormal glucose tolerance during pregnancy	O24.9	Non specified diabetes during pregnancy
Secondary	5770	Acute pancreatitis	K85	Acute pancreatitis
DM	5771	Chronic pancreatitis	K86	Acute and chronic pancreatitis caused by consumption of alcohol
	5779	Non-specified disease of the pancreas		Non-specified disease of the pancreas
			K86.3	
			K87.1	Disease of the pancreas related to other disease
			K90.3	Pancreatic steatorrhea
	0723A	Pancreatitis caused by mumps	B26.3	Pancreatitis caused by mumps
	157	Cancer of the pancreas	C25	Cancer of the pancreas
	2530A	Acromegaly	E22.0	Acromegaly
	2550A	Cushing's syndrome	E24	Cushing's syndrome
			E31.00	APECED syndrome
	2750	Hemochromatosis	E83.1	Disorders of iron metabolism
	2751	Wilson's disease	E83.0	Disorders of copper metabolism
	2770A	Cystic fibrosis	E84	Cystic fibrosis
	5710-5713	Alcoholic liver disease	K70	Alcoholic liver disease

Secondary	7517A	Malformation of the pancreas	Q45.0-Q45.3	Malformation of the pancreas
DM	7580A	Down's syndrome	Q90	Down's syndrome
	8680A	Lesion of abdominal organ (other than gastro-intestinal tract, liver, spleen or kidney)	S36.2	Lesion of the pancreas
	2513A	Postoperative hypoinsulinemia	E89.1	Iatrogenic hypoinsulinemia